A 48-year-old woman comes to the office for follow-up of primary hypothyroidism due to chronic autoimmune (Hashimoto) thyroiditis. She feels well and has no palpitations, heat/cold intolerance, diarrhea/constipation, or changes in weight. The patient takes levothyroxine daily on an empty stomach. She has no other medical conditions and takes no other medications. The patient has no drug allergies and does not use tobacco, alcohol, or illicit drugs. Blood pressure is 120/70 mm Hg and pulse is 72/min. BMI is 27 kg/m^2. On physical examination, the thyroid is normal to palpation. There is no peripheral edema. Laboratory results show a serum TSH level of <0.01 μU/mL. Maintaining the current dose of levothyroxine would put this patient at the greatest risk for which of the following complications?

- A. Agranulocytosis
- B. Atrial fibrillation
- C. Dementia
- D. Goiter
- E. Hepatotoxicity
- F. Thyroid cancer

Submit

A 48-year-old woman comes to the office for follow-up of primary hypothyroidism due to chronic autoimmune (Hashimoto) thyroiditis. She feels well and has no palpitations, heat/cold intolerance, diarrhea/constipation, or changes in weight. The patient takes levothyroxine daily on an empty stomach. She has no other medical conditions and takes no other medications. The patient has no drug allergies and does not use tobacco, alcohol, or illicit drugs. Blood pressure is 120/70 mm Hg and pulse is 72/min. BMI is 27 kg/m^2. On physical examination, the thyroid is normal to palpation. There is no peripheral edema. Laboratory results show a serum TSH level of <0.01 μU/mL. Maintaining the current dose of levothyroxine would put this patient at the greatest risk for which of the following complications?

- A. Agranulocytosis (13%)
- ✓ B. Atrial fibrillation (53%)
- C. Dementia (2%)
- D. Goiter (17%)
- E. Hepatotoxicity (8%)
- F. Thyroid cancer (4%)

Omitted
Correct answer
B

53%
Answered correctly

04 secs
Time Spent

02/05/2020
Last Updated

Explanation

Cardiovascular effects of hyperthyroidism	
	• Tachycardia/palpitations

Cardiovascular effects of hyperthyroidism	
Increased rate	• Tachycardia/palpitations • Atrial fibrillation
Increased contractility	• ↑ Ejection fraction & cardiac output • ↑ Myocardial oxygen demand & angina • ↑ Pulmonary artery pressure
Decreased afterload	• ↓ Systemic vascular resistance
Additional effects	• ↓ Diastolic pressure • ↑ Systolic pressure • ↑ Pulse pressure • High-output heart failure

This patient is on **thyroid replacement therapy** for hypothyroidism and has a **suppressed TSH** (normal range: 0.5 to 5.0 μU/mL), indicating that her **current dose is too high**. Excess thyroid hormone, whether due to endogenous hyperthyroidism or iatrogenic over-replacement with levothyroxine, causes increased beta-adrenergic receptor expression. The resulting **hyperadrenergic state** can lead to significant cardiovascular complications.

Thyrotoxicosis is associated with hypertension, tachycardia, and increased myocyte automaticity. **Atrial fibrillation** is the most common supraventricular arrhythmia and is a frequent complication of thyrotoxicosis. Thyrotoxicosis also increases contractility, which increases myocardial oxygen demand and can **precipitate angina** in patients with underlying coronary disease. It can also increase cardiac output (while also decreasing systemic vascular resistance) and lead to **high-output heart failure**. Therefore, even though this patient feels well, her dose of levothyroxine should be reduced to avoid long-term complications of over-replacement.

(Choices A and E) Agranulocytosis is a potential complication of thionamide antithyroid drugs (eg, propylthiouracil, methimazole). Propylthiouracil can also cause hepatotoxicity. However, levothyroxine used in thyroid replacement therapy does not cause these complications.

(Choice C) Thyroid over-replacement can cause insomnia and affective symptoms (eg, anxiety, irritability). Although hyperthyroidism in elderly

This patient is on **thyroid replacement therapy** for hypothyroidism and has a **suppressed TSH** (normal range: 0.5 to 5.0 μU/mL), indicating that her **current dose is too high**. Excess thyroid hormone, whether due to endogenous hyperthyroidism or iatrogenic over-replacement with levothyroxine, causes increased beta-adrenergic receptor expression. The resulting **hyperadrenergic state** can lead to significant cardiovascular complications.

Thyrotoxicosis is associated with hypertension, tachycardia, and increased myocyte automaticity. **Atrial fibrillation** is the most common supraventricular arrhythmia and is a frequent complication of thyrotoxicosis. Thyrotoxicosis also increases contractility, which increases myocardial oxygen demand and can **precipitate angina** in patients with underlying coronary disease. It can also increase cardiac output (while also decreasing systemic vascular resistance) and lead to **high-output heart failure**. Therefore, even though this patient feels well, her dose of levothyroxine should be reduced to avoid long-term complications of over-replacement.

(Choices A and E) Agranulocytosis is a potential complication of thionamide antithyroid drugs (eg, propylthiouracil, methimazole). Propylthiouracil can also cause hepatotoxicity. However, levothyroxine used in thyroid replacement therapy does not cause these complications.

(Choice C) Thyroid over-replacement can cause insomnia and affective symptoms (eg, anxiety, irritability). Although hyperthyroidism in elderly patients may manifest as social withdrawal and slowed responses (apathetic depression) resembling dementia, cognitive dysfunction in younger patients is more likely to be seen in hypothyroidism rather than in hyperthyroidism.

(Choice D) The goiter seen in hypothyroidism is due to chronic thyroid stimulation by TSH. This manifestation improves with the administration of levothyroxine (as TSH levels are decreased) and is not seen in over-replacement.

(Choice F) Thyroid cancer is a potential long-term complication of radioiodine therapy for hyperthyroidism.

Educational objective:
Thyrotoxicosis, whether due to endogenous hyperthyroidism or over-replacement with thyroid hormone in patients with hypothyroidism, causes a hyperadrenergic state that can lead to atrial fibrillation, high-output heart failure, and worsening of angina pectoris.

References

- Cardiovascular disease and thyroid function.

Pathophysiology Endocrine, Diabetes & Metabolism Hypothyroidism

complications.

Thyrotoxicosis is associated with hypertension, tachycardia, and increased myocyte automaticity. **Atrial fibrillation** is the most common supraventricular arrhythmia and is a frequent complication of thyrotoxicosis. Thyrotoxicosis also increases contractility, which increases myocardial oxygen demand and can **precipitate angina** in patients with underlying coronary disease. It can also increase cardiac output (while also decreasing systemic vascular resistance) and lead to **high-output heart failure**. Therefore, even though this patient feels well, her dose of levothyroxine should be reduced to avoid long-term complications of over-replacement.

(Choices A and E) Agranulocytosis is a potential complication of thionamide antithyroid drugs (eg, propylthiouracil, methimazole). Propylthiouracil can also cause hepatotoxicity. However, levothyroxine used in thyroid replacement therapy does not cause these complications.

(Choice C) Thyroid over-replacement can cause insomnia and affective symptoms (eg, anxiety, irritability). Although hyperthyroidism in elderly patients may manifest as social withdrawal and slowed responses (apathetic depression) resembling dementia, cognitive dysfunction in younger patients is more likely to be seen in hypothyroidism rather than in hyperthyroidism.

(Choice D) The goiter seen in hypothyroidism is due to chronic thyroid stimulation by TSH. This manifestation improves with the administration of levothyroxine (as TSH levels are decreased) and is not seen in over-replacement.

(Choice F) Thyroid cancer is a potential long-term complication of radioiodine therapy for hyperthyroidism.

Educational objective:
Thyrotoxicosis, whether due to endogenous hyperthyroidism or over-replacement with thyroid hormone in patients with hypothyroidism, causes a hyperadrenergic state that can lead to atrial fibrillation, high-output heart failure, and worsening of angina pectoris.

References

- Cardiovascular disease and thyroid function.

Pathophysiology	Endocrine, Diabetes & Metabolism	Hypothyroidism
Subject	System	Topic

Copyright © UWorld. All rights reserved.

A 60-year-old man is brought to the emergency department due to altered mental status. His wife says that he had a nagging cough that seemed to worsen over the past several months and that he began experiencing occasional dizziness earlier this week. Over the last couple of days, the patient has become increasingly confused, and today he "does not make any sense at all." He has no significant past medical history but has smoked a pack of cigarettes daily for the last 40 years. On physical examination, the patient is incoherent but has an otherwise normal neurologic examination.

Laboratory results are as follows:

Serum chemistry	
Sodium	120 mEq/L
Potassium	4.0 mEq/L
Blood urea nitrogen	12 mg/dL
Creatinine	0.8 mg/dL
Calcium	9.0 mg/dL
Glucose	98 mg/dL
Plasma osmolality	250 mOsm/kg
Urine drug screen	negative

Chest x-ray reveals a mass in the right lung. Which of the following additional findings is most likely to be present in this patient?

A. Bilateral crackles at the lung bases
B. Elevated jugular venous pressure
C. Maximally dilute urine

Serum chemistry	
Sodium	120 mEq/L
Potassium	4.0 mEq/L
Blood urea nitrogen	12 mg/dL
Creatinine	0.8 mg/dL
Calcium	9.0 mg/dL
Glucose	98 mg/dL
Plasma osmolality	250 mOsm/kg
Urine drug screen	negative

Chest x-ray reveals a mass in the right lung. Which of the following additional findings is most likely to be present in this patient?

A. Bilateral crackles at the lung bases
B. Elevated jugular venous pressure
C. Maximally dilute urine
D. Apparent euvolemia
E. Peripheral edema

Submit

Serum chemistry	
Sodium	120 mEq/L
Potassium	4.0 mEq/L
Blood urea nitrogen	12 mg/dL
Creatinine	0.8 mg/dL
Calcium	9.0 mg/dL
Glucose	98 mg/dL
Plasma osmolality	250 mOsm/kg
Urine drug screen	negative

Chest x-ray reveals a mass in the right lung. Which of the following additional findings is most likely to be present in this patient?

A. Bilateral crackles at the lung bases (5%)
B. Elevated jugular venous pressure (11%)
C. Maximally dilute urine (19%)
✓ D. Apparent euvolemia (45%)
E. Peripheral edema (18%)

Omitted
Correct answer

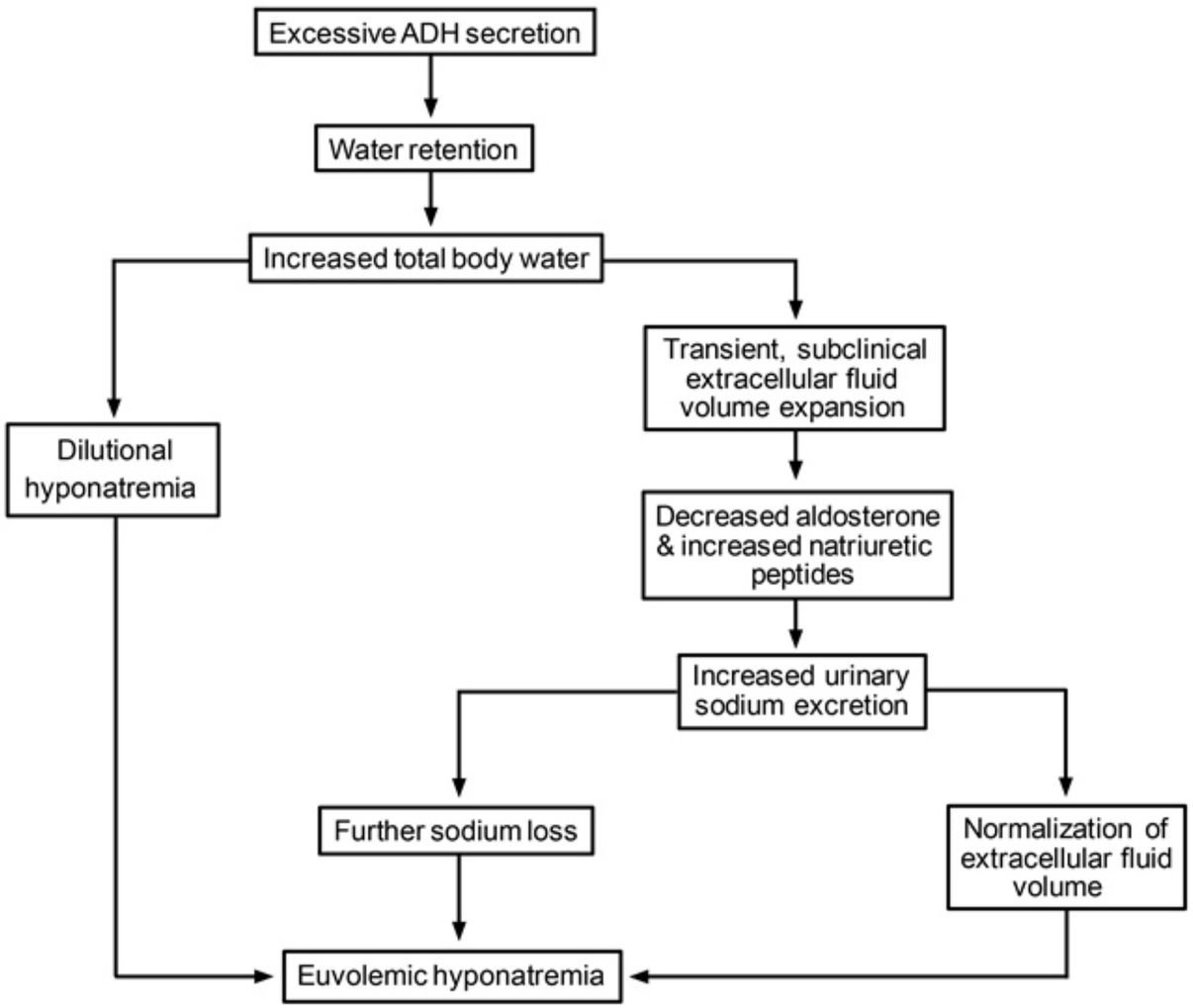
45%
Answered correctly

06 secs
Time Spent

03/03/2020
Last Updated

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31

Pathophysiology of SIADH



SIADH = syndrome of inappropriate antidiuretic hormone.

©UWorld

The combination of hyponatremia and a lung mass is suggestive of the **syndrome of inappropriate antidiuretic hormone secretion** (SIADH). ADH is normally produced in the hypothalamus and secreted from the posterior pituitary in response to changes in plasma osmolality and intravascular volume. However, **small cell lung carcinomas**, which are tumors of neuroendocrine origin, often release ADH independent of feedback inhibition (paraneoplastic effect). This inappropriate secretion of ADH leads to hyponatremia, decreased plasma osmolality, and elevated urine osmolality (which normally should be <100 mOsm/kg given the degree of hyponatremia). The profound hyponatremia that occurs in SIADH can cause headache, weakness, **altered mental status**, and seizures.

In SIADH, increased ADH causes excessive water absorption by the kidneys, leading to a transient, subclinical hypervolemia. This mild increase in extracellular fluid volume suppresses the renin-aldosterone axis and stimulates the production of natriuretic peptides, leading to excretion of sodium in the urine (natriuresis). As a result, patients with SIADH have a clinically normal extracellular fluid volume and low plasma osmolality (**euvolemic hyponatremia**). Features of volume overload (eg, peripheral edema, pulmonary crackles, elevated jugular venous pressure) are not seen **(Choices A, B, and E)**.

(Choice C) Patients with SIADH have inappropriately concentrated urine (generally >100 mOsm/kg) for their degree of hyponatremia. Hyponatremia with a urine osmolality of <100 mOsm/kg (maximally dilute urine) indicates appropriate suppression of ADH secretion (as would be seen in primary polydipsia).

Educational objective:
The syndrome of inappropriate antidiuretic hormone secretion (SIADH) is characterized by low plasma sodium and osmolality, inappropriately concentrated urine, and clinically normal volume status (euvolemic hyponatremia). An important cause of SIADH is a paraneoplastic effect secondary to small cell carcinoma of the lung.

References

- The syndrome of inappropriate antidiuresis: pathophysiology, clinical management and new therapeutic options.
- Management of hyponatremia: providing treatment and avoiding harm.

Pathophysiology	Endocrine, Diabetes & Metabolism	SIADH
Subject	System	Topic

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31

A 22-year-old man comes to the office for evaluation of a neck mass. He first noticed a small nodule in his lower neck 6 months ago, and it has progressively enlarged since that time. The patient has had no changes in weight and otherwise feels well. Medical history is notable only for seasonal allergies, and he takes no medications. Physical examination shows a 2-cm nodule in the right lobe of the thyroid. There are multiple 4- to 8-mm soft papules on the lips and tongue. The arm span exceeds his height and the patient has long fingers. Serum calcitonin levels are elevated. Which of the following is most likely to develop in this patient?

A. Episodic headache

B. Hypercalcemia

C. Hypoglycemic episodes

D. Peripheral vision loss

E. Recurrent peptic ulcers

Submit

A 22-year-old man comes to the office for evaluation of a neck mass. He first noticed a small nodule in his lower neck 6 months ago, and it has progressively enlarged since that time. The patient has had no changes in weight and otherwise feels well. Medical history is notable only for seasonal allergies, and he takes no medications. Physical examination shows a 2-cm nodule in the right lobe of the thyroid. There are multiple 4- to 8-mm soft papules on the lips and tongue. The arm span exceeds his height and the patient has long fingers. Serum calcitonin levels are elevated. Which of the following is most likely to develop in this patient?

- ✓ A. Episodic headache (65%)
- B. Hypercalcemia (14%)
- C. Hypoglycemic episodes (5%)
- D. Peripheral vision loss (8%)
- E. Recurrent peptic ulcers (5%)

Omitted
Correct answer
A

65%
Answered correctly

02 secs
Time Spent

05/22/2020
Last Updated

Explanation

Classification of multiple endocrine neoplasia	
Type 1	• **Primary hyperparathyroidism** (parathyroid adenomas or hyperplasia) • Pituitary tumors (prolactin, visual defects)

Explanation

Classification of multiple endocrine neoplasia	
Type 1	• **Primary hyperparathyroidism** (parathyroid adenomas or hyperplasia) • Pituitary tumors (prolactin, visual defects) • Pancreatic tumors (especially gastrinomas)
Type 2A	• **Medullary thyroid cancer** (calcitonin) • Pheochromocytoma • Primary hyperparathyroidism (parathyroid hyperplasia)
Type 2B	• **Medullary thyroid cancer** (calcitonin) • Pheochromocytoma • Mucosal neuromas/marfanoid habitus

This patient has an enlarging thyroid nodule associated with an elevated calcitonin level, which is concerning for **medullary thyroid cancer** (MTC), a malignancy arising from the thyroid C (parafollicular) cells. These findings, in association with mucosal neuromas and **marfanoid habitus** (eg, arm span > height, long fingers, joint laxity), suggest **multiple endocrine neoplasia type 2B** (MEN2B). MEN2 syndromes are caused by germline mutations of the ***RET*** proto-oncogene. MTC is present in nearly all patients with MEN2 and is usually more aggressive and occurs at an earlier age than sporadic MTC.

Pheochromocytomas develop in roughly half of patients with MEN2 syndromes and cause paroxysmal hypertension and tachycardia due to the intermittent secretion of catecholamines. The abrupt, severe increase in blood pressure can precipitate **episodic headaches** and is often accompanied by other symptoms associated with catecholamine excess (eg, diaphoresis, tremor, chest pain).

(Choice B) Hyperparathyroidism with secondary hypercalcemia is the most common manifestation of MEN1. Hyperparathyroidism (due to parathyroid chief cell hyperplasia or adenoma formation) is also seen in 10%-20% of patients with MEN2A, but it is not a feature of MEN2B.

(Choices C and E) Many patients with MEN1 have endocrine pancreatic tumors that secrete gastrin, leading to refractory peptic ulceration and

	• Mucosal neuromas/marfanoid habitus

This patient has an enlarging thyroid nodule associated with an elevated calcitonin level, which is concerning for **medullary thyroid cancer** (MTC), a malignancy arising from the thyroid C (parafollicular) cells. These findings, in association with mucosal neuromas and **marfanoid habitus** (eg, arm span > height, long fingers, joint laxity), suggest **multiple endocrine neoplasia type 2B** (MEN2B). MEN2 syndromes are caused by germline mutations of the ***RET*** proto-oncogene. MTC is present in nearly all patients with MEN2 and is usually more aggressive and occurs at an earlier age than sporadic MTC.

Pheochromocytomas develop in roughly half of patients with MEN2 syndromes and cause paroxysmal hypertension and tachycardia due to the intermittent secretion of catecholamines. The abrupt, severe increase in blood pressure can precipitate **episodic headaches** and is often accompanied by other symptoms associated with catecholamine excess (eg, diaphoresis, tremor, chest pain).

(Choice B) Hyperparathyroidism with secondary hypercalcemia is the most common manifestation of MEN1. Hyperparathyroidism (due to parathyroid chief cell hyperplasia or adenoma formation) is also seen in 10%-20% of patients with MEN2A, but it is not a feature of MEN2B.

(Choices C and E) Many patients with MEN1 have endocrine pancreatic tumors that secrete gastrin, leading to refractory peptic ulceration and diarrhea (Zollinger-Ellison syndrome). In rare cases, endocrine tumors of the pancreas in MEN1 secrete other hormones, such as insulin, which can cause hypoglycemia.

(Choice D) Pituitary tumors are present in 50% of patients with MEN1. Large pituitary tumors with suprasellar extensions are likely to cause peripheral vision loss.

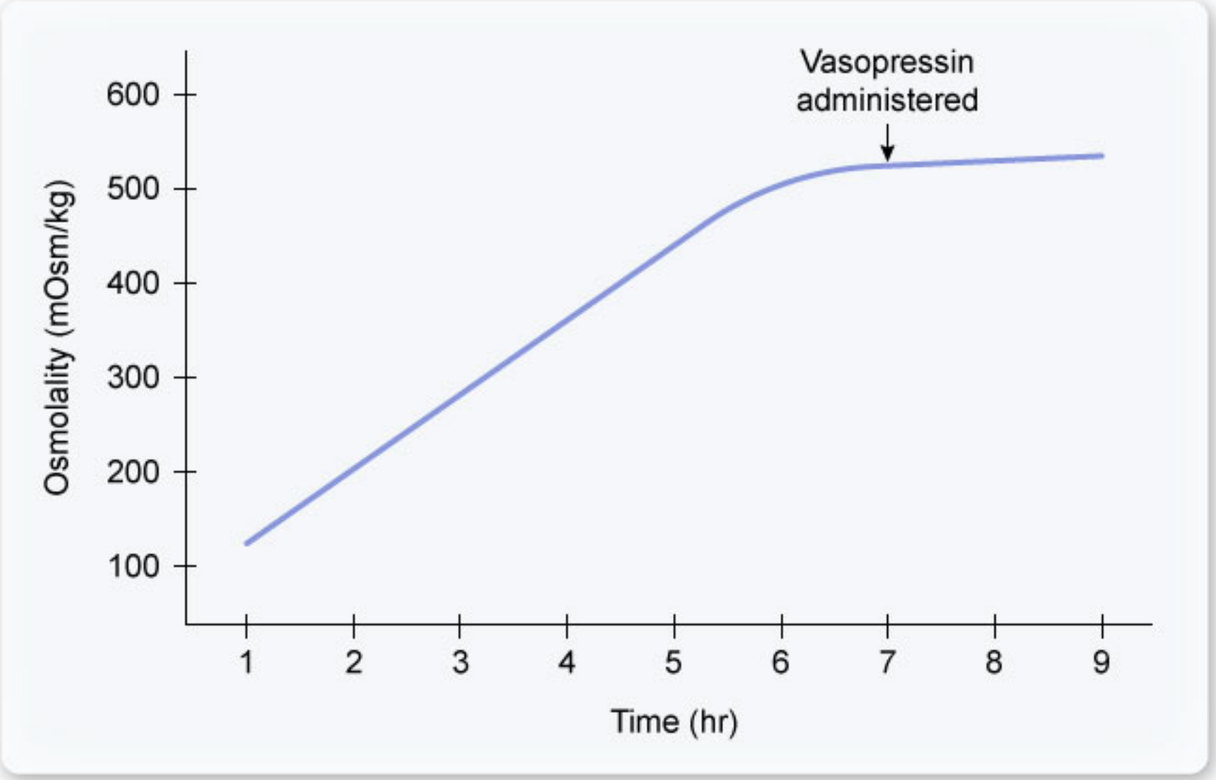
Educational objective:
Multiple endocrine neoplasia type 2B is characterized by medullary thyroid cancer, pheochromocytomas, mucosal neuromas, and marfanoid habitus. Hyperparathyroidism is not a feature of this syndrome.

References

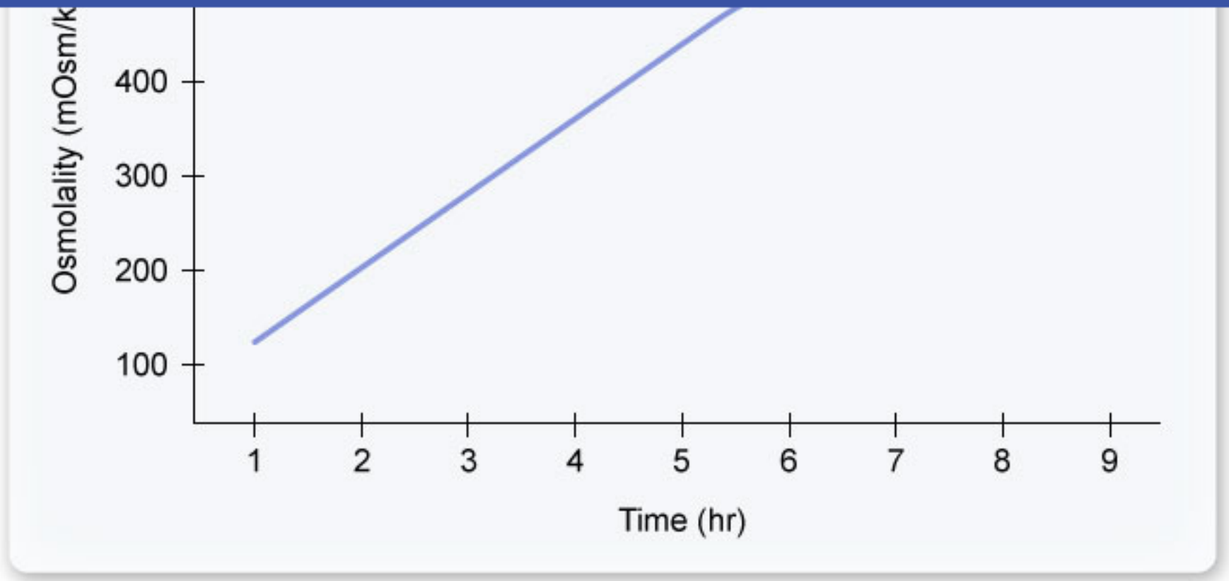
- 2012 European Thyroid Association guidelines for genetic testing and its clinical consequences in medullary thyroid cancer.
- Revised American Thyroid Association guidelines for the management of medullary thyroid carcinoma.

Pathophysiology Endocrine, Diabetes & Metabolism Multiple endocrine neoplasia

A 28-year-old woman comes to the clinic due to generalized weakness and frequent, high-volume urination. She has had no dysuria, hematuria, or abdominal pain. The patient's symptoms have been ongoing for several months, but she cannot recall exactly when they began. She has no other medical conditions. The patient is a single mother of a 2-year-old child, has little social support, and occasionally uses alcohol and marijuana "to cope with the stress." Vital signs and physical examination are normal. Blood glucose is 95 mg/dL and serum sodium is 132 mEq/L. Urinalysis shows no white or red blood cells. During further evaluation, urine osmolality is serially measured while fluid intake is restricted; vasopressin is subsequently administered 7 hours into the test. The results are shown below.



©UWorld



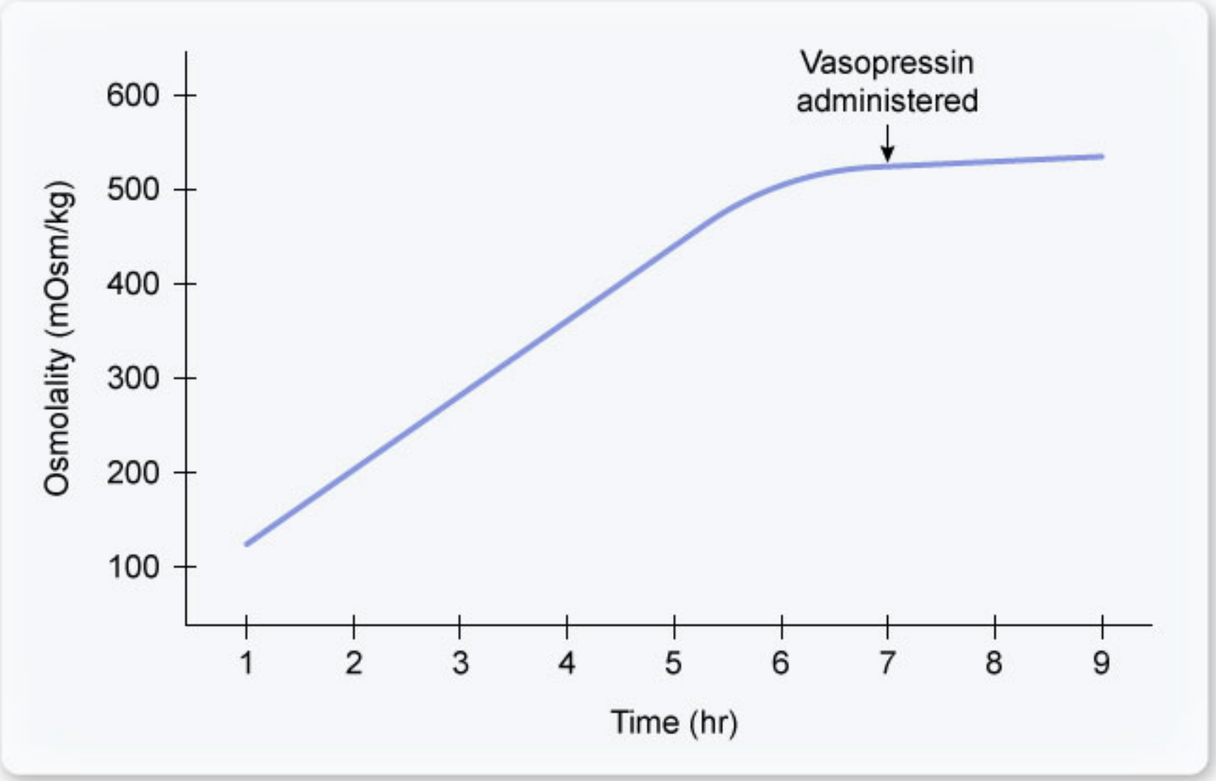
©UWorld

Which of the following is the most appropriate long-term treatment for this patient?

- A. Desmopressin
- B. Hydrochlorothiazide
- C. Indomethacin
- D. Insulin
- E. Water restriction

Submit

mEq/L. Urinalysis shows no white or red blood cells. During further evaluation, urine osmolality is serially measured while fluid intake is restricted; vasopressin is subsequently administered 7 hours into the test. The results are shown below.

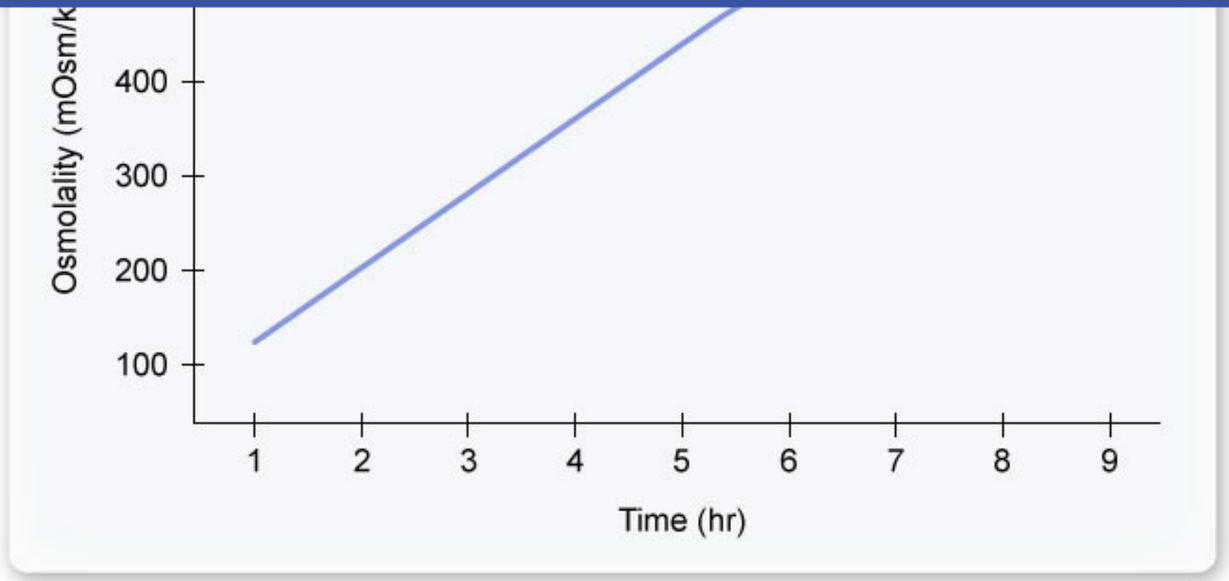


©UWorld

Which of the following is the most appropriate long-term treatment for this patient?

A. Desmopressin

B. Hydrochlorothiazide



©UWorld

Which of the following is the most appropriate long-term treatment for this patient?

A. Desmopressin (29%)

B. Hydrochlorothiazide (13%)

C. Indomethacin (3%)

D. Insulin (1%)

✓ E. Water restriction (51%)

Omitted
Correct answer

51%
Answered correctly

47 secs
Time Spent

06/06/2020
Last Updated

Polyuria & polydipsia			
		Water deprivation test	
	Serum sodium	Urine osmolality after water deprivation	Urine osmolality with vasopressin injection
Normal	Normal	Increased	No additional increase
Central diabetes insipidus	High	No change or mild increase	Large increase
Nephrogenic diabetes insipidus	High	No change or mild increase	Mild increase
Primary polydipsia	Low	Increased	No additional increase

This patient has **polyuria** (urine output >3 L/day) with a **low initial urine osmolality**, which is indicative of **water diuresis** caused by one of the following conditions:

- Diabetes insipidus (DI), which occurs due to either deficient antidiuretic hormone (ADH) production (central DI) or lack of renal response to ADH (nephrogenic DI)
- Primary polydipsia, which results from excessive water consumption (most common in patients with underlying psychiatric disease or emotional distress)

In patients with **primary polydipsia**, excessive water intake often leads to mild **hyponatremia**. In contrast, primary ADH deficiency in DI leads to free water loss often with ensuing hypernatremia. In certain patients, water deprivation testing may be helpful for differentiating PP from DI.

During a **water deprivation test**, drinking water is withheld and urine osmolality is monitored until it reaches a steady-state plateau (representing the maximal concentrating ability of the kidneys). Water deprivation in patients with PP stimulates ADH secretion and leads to a significant **rise in urine concentration**, whereas urine in patients with DI remains dilute. Once a plateau is reached, **vasopressin is administered**. In DI, exogenous vasopressin causes an increase in urine osmolality; in PP, urine **concentration remains unchanged** because at this point in the test, the endogenous ADH effect is already at maximum.

following conditions:

- Diabetes insipidus (DI), which occurs due to either deficient antidiuretic hormone (ADH) production (central DI) or lack of renal response to ADH (nephrogenic DI)
- Primary polydipsia, which results from excessive water consumption (most common in patients with underlying psychiatric disease or emotional distress)

In patients with **primary polydipsia**, excessive water intake often leads to mild **hyponatremia**. In contrast, primary ADH deficiency in DI leads to free water loss often with ensuing hypernatremia. In certain patients, water deprivation testing may be helpful for differentiating PP from DI.

During a **water deprivation test**, drinking water is withheld and urine osmolality is monitored until it reaches a steady-state plateau (representing the maximal concentrating ability of the kidneys). Water deprivation in patients with PP stimulates ADH secretion and leads to a significant **rise in urine concentration**, whereas urine in patients with DI remains dilute. Once a plateau is reached, **vasopressin is administered**. In DI, exogenous vasopressin causes an increase in urine osmolality; in PP, urine **concentration remains unchanged** because at this point in the test, the endogenous ADH effect is already at maximum.

If PP is confirmed, long-term management includes **restriction of free water** intake.

(Choices A, B, and C) Central DI can be treated with desmopressin (synthetic ADH analog), while nephrogenic DI is typically treated with thiazide diuretics (induce mild hypovolemia that decreases polyuria) or NSAIDs (inhibit renal prostaglandins that act as ADH antagonists). However, during water deprivation, patients with central or nephrogenic DI typically have no change or only a mild increase in urine osmolality due to lack of adequate ADH effect; subsequent vasopressin administration would also be expected to cause an increase in urine osmolality.

(Choice D) Severe hyperglycemia in diabetes mellitus can overwhelm the ability of the kidneys to recover the filtered glucose load, leading to osmotic diuresis and polyuria. However, this typically occurs with blood glucose >180 mg/dL; this patient's glucose is normal.

Educational objective:
Primary (psychogenic) polydipsia is characterized by excessive intake of free water, leading to hyponatremia and production of large volumes of dilute urine. Water restriction normalizes serum sodium levels and increases urine osmolality.

References

- The water deprivation test and a potential role for the arginine vasopressin precursor copeptin to differentiate diabetes insipidus from primary polydipsia.

A 30-year-old woman comes to the office due to generalized weakness and paresthesia. Medical history is unremarkable and she takes no medications. However, the patient says her blood pressure was elevated at a workplace health fair 3 months ago, although she attributed it to being "stressed out" and did not take any action. Blood pressure is 150/95 mm Hg. Cardiac examination is normal with full and symmetric distal pulses and no pedal edema. Laboratory evaluation shows low plasma renin activity and normal serum creatinine levels. CT scan of the abdomen reveals a solitary, hypodense, 1.5-cm right adrenal mass. Which of the following patterns of serum electrolyte concentrations would most likely be seen in this patient?

	Sodium	Potassium	Bicarbonate
A.	High	Low	Low
B.	Low	High	Low
C.	Low	Low	High
D.	Normal	High	Low
E.	Normal	Low	High

Submit

A 30-year-old woman comes to the office due to generalized weakness and paresthesia. Medical history is unremarkable and she takes no medications. However, the patient says her blood pressure was elevated at a workplace health fair 3 months ago, although she attributed it to being "stressed out" and did not take any action. Blood pressure is 150/95 mm Hg. Cardiac examination is normal with full and symmetric distal pulses and no pedal edema. Laboratory evaluation shows low plasma renin activity and normal serum creatinine levels. CT scan of the abdomen reveals a solitary, hypodense, 1.5-cm right adrenal mass. Which of the following patterns of serum electrolyte concentrations would most likely be seen in this patient?

	Sodium	Potassium	Bicarbonate
A. (51%)	High	Low	Low
B. (9%)	Low	High	Low
C. (2%)	Low	Low	High
D. (2%)	Normal	High	Low
✓ E. (33%)	Normal	Low	High

Omitted
Correct answer
E

33%
Answered correctly

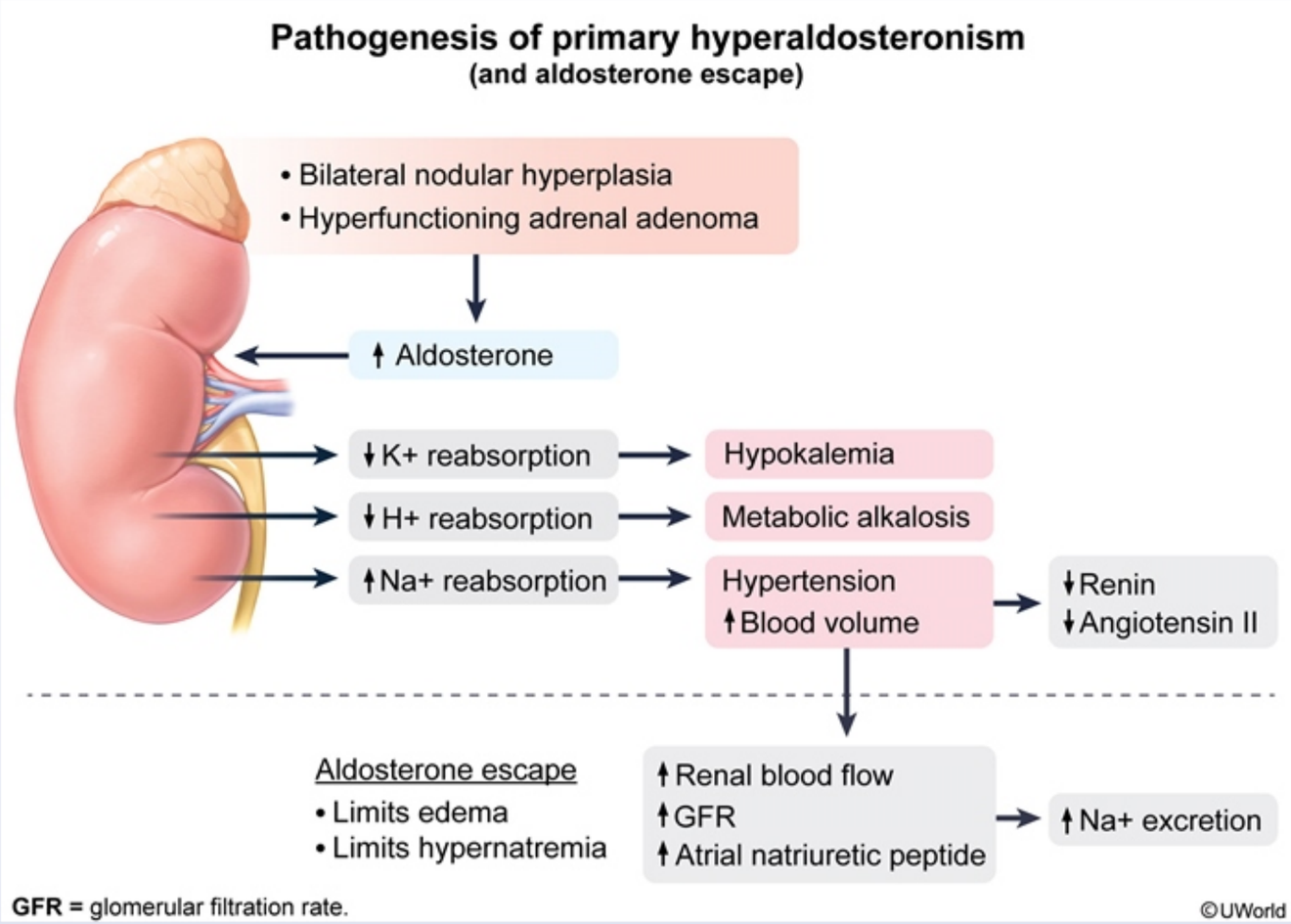
01 sec
Time Spent

03/27/2020
Last Updated

Explanation

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31

Explanation



This patient has **hypertension** at a young age, suggesting a **secondary** cause. Her weakness and paresthesia indicate an associated electrolyte or acid-base disturbance. These findings, along with a suppressed plasma renin, suggest **primary mineralocorticoid excess (hyperaldosteronism)**. The most common causes of primary hyperaldosteronism include **unilateral adrenal adenoma** (Conn syndrome) and bilateral adrenal hyperplasia (idiopathic hyperaldosteronism), which can be differentiated on abdominal CT scan.

GFR = glomerular filtration rate.

©UWorld

This patient has **hypertension** at a young age, suggesting a **secondary** cause. Her weakness and paresthesia indicate an associated electrolyte or acid-base disturbance. These findings, along with a suppressed plasma renin, suggest **primary mineralocorticoid excess (hyperaldosteronism)**. The most common causes of primary hyperaldosteronism include **unilateral adrenal adenoma** (Conn syndrome) and bilateral adrenal hyperplasia (idiopathic hyperaldosteronism), which can be differentiated on abdominal CT scan.

Hyperaldosteronism is characterized by increased Na^+ reabsorption in the renal collecting tubules. This creates a negative charge in the lumen, pulling K^+ and H^+ from tubular cells and leading to increased excretion of urinary K^+ and H^+. As a result, **hypokalemia** is common. Increased H^+ excretion by α-intercalated cells promotes bicarbonate production and increased activity of the basolateral HCO_3^-/Cl- exchanger, resulting in elevated serum bicarbonate and **metabolic alkalosis**.

Despite the increase in Na^+ reabsorption, hypernatremia and pedal edema are rarely observed due to a phenomenon known as **aldosterone escape**. The increased intravascular volume causes increased renal blood flow (with resulting pressure natriuresis) and augmented release of atrial natriuretic peptide. This limits net sodium retention and prevents the development of overt volume overload and significant hypernatremia.

(Choice A) Due to aldosterone escape, serum Na^+ concentration is normal in hyperaldosteronism. Increased loss of K^+ and H^+ in the urine causes hypokalemia and high (not low) serum bicarbonate.

(Choice B) Patients with primary adrenal insufficiency have increased renal Na^+ loss and reduced urinary excretion of K^+ and H^+ due to low aldosterone activity. As a result, hypovolemia, hyponatremia, hyperkalemia, and metabolic acidosis develop. Hypovolemia also acts as a nonosmotic stimulus for antidiuretic hormone (ADH) secretion, further accentuating the hyponatremia.

(Choice C) Loop or thiazide diuretic use can cause hypovolemia, hyponatremia (mostly with thiazides), hypokalemia, and metabolic alkalosis due to urinary losses of Na^+, K^+, and H^+. Hypovolemia can also exacerbate hyponatremia (due to increased ADH secretion) and alkalosis (due to increased bicarbonate reabsorption).

(Choice D) Mineralocorticoid receptor antagonists (eg, spironolactone) block aldosterone receptors and impair urinary excretion of K^+ and H^+. Side effects include hyperkalemia and metabolic acidosis. Na^+ excretion is only mildly increased and serum Na^+ concentration is usually not significantly affected.

Educational objective:

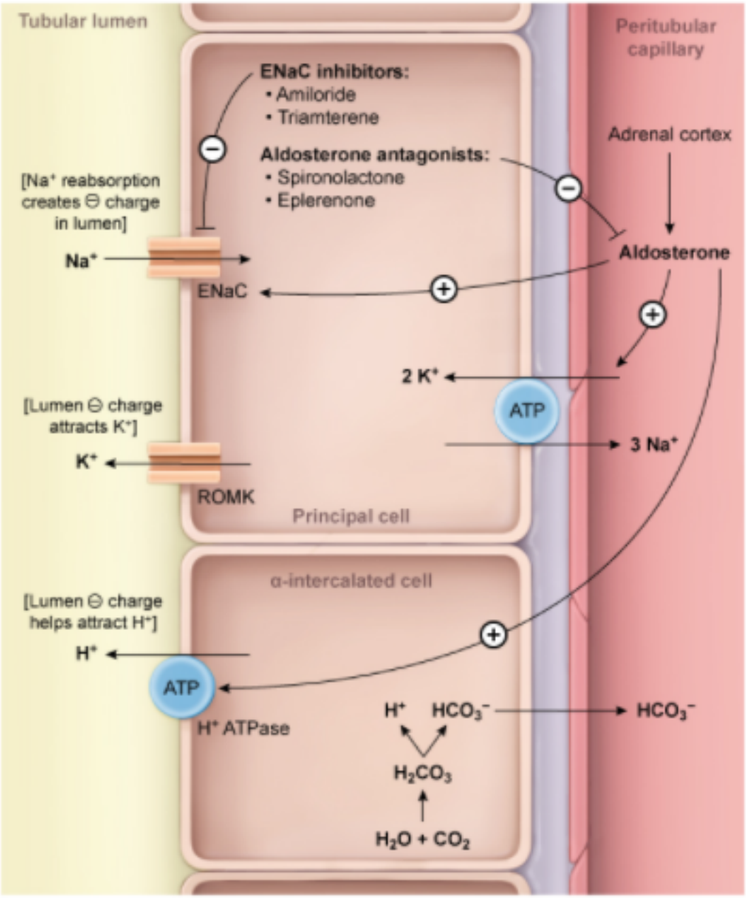
Primary hyperaldosteronism causes increased Na^+ reabsorption in the renal collecting tubules, leading to increased urinary excretion of K^+ and

GFR = glomerular filtration rate.

©UWorld

Exhibit Display

Action of aldosterone in the collecting duct of the nephron



©UWorld

Zoom In | Zoom Out | Reset | Add To New Card | Existing Card

Primary hyperaldosteronism causes increased Na^+ reabsorption in the renal collecting tubules, leading to increased urinary excretion of K^+ and

Despite the increase in Na^+ reabsorption, hypernatremia and pedal edema are rarely observed due to a phenomenon known as **aldosterone escape**. The increased intravascular volume causes increased renal blood flow (with resulting pressure natriuresis) and augmented release of atrial natriuretic peptide. This limits net sodium retention and prevents the development of overt volume overload and significant hypernatremia.

(Choice A) Due to aldosterone escape, serum Na^+ concentration is normal in hyperaldosteronism. Increased loss of K^+ and H^+ in the urine causes hypokalemia and high (not low) serum bicarbonate.

(Choice B) Patients with primary adrenal insufficiency have increased renal Na^+ loss and reduced urinary excretion of K^+ and H^+ due to low aldosterone activity. As a result, hypovolemia, hyponatremia, hyperkalemia, and metabolic acidosis develop. Hypovolemia also acts as a nonosmotic stimulus for antidiuretic hormone (ADH) secretion, further accentuating the hyponatremia.

(Choice C) Loop or thiazide diuretic use can cause hypovolemia, hyponatremia (mostly with thiazides), hypokalemia, and metabolic alkalosis due to urinary losses of Na^+, K^+, and H^+. Hypovolemia can also exacerbate hyponatremia (due to increased ADH secretion) and alkalosis (due to increased bicarbonate reabsorption).

(Choice D) Mineralocorticoid receptor antagonists (eg, spironolactone) block aldosterone receptors and impair urinary excretion of K^+ and H^+. Side effects include hyperkalemia and metabolic acidosis. Na^+ excretion is only mildly increased and serum Na^+ concentration is usually not significantly affected.

Educational objective:
Primary hyperaldosteronism causes increased Na^+ reabsorption in the renal collecting tubules, leading to increased urinary excretion of K^+ and H^+. Patients typically have secondary hypertension as well as hypokalemia and metabolic alkalosis. The serum Na+ concentration remains normal due to aldosterone escape.

References

- Mineralocorticoid hypertension and hypokalemia.

Pathophysiology	Endocrine, Diabetes & Metabolism	Hyperaldosteronism
Subject	System	Topic

Copyright © UWorld. All rights reserved.

A 55-year-old woman comes to the office due to increasing fatigability and a 4.54-kg (10-lb) weight gain over the last few months. The patient used to swim daily but now does so only once or twice a week due to fatigue. She takes a daily multivitamin and an over-the-counter medication for constipation. Blood pressure is 140/96 mm Hg and pulse is 55/min. Physical examination shows hair loss involving the lateral third of the eyebrows. There is delayed relaxation of the deep tendon reflexes of the knee and ankle. Which of the following laboratory tests is the most appropriate next step in evaluation of this patient's symptoms?

- A. 24-hour urinary cortisol excretion test
- B. Dexamethasone suppression test
- C. Fasting plasma glucose level
- D. Serum iron studies
- E. Serum triiodothyronine and thyroxine levels
- F. Serum TSH level

Submit

A 55-year-old woman comes to the office due to increasing fatigability and a 4.54-kg (10-lb) weight gain over the last few months. The patient used to swim daily but now does so only once or twice a week due to fatigue. She takes a daily multivitamin and an over-the-counter medication for constipation. Blood pressure is 140/96 mm Hg and pulse is 55/min. Physical examination shows hair loss involving the lateral third of the eyebrows. There is delayed relaxation of the deep tendon reflexes of the knee and ankle. Which of the following laboratory tests is the most appropriate next step in evaluation of this patient's symptoms?

- A. 24-hour urinary cortisol excretion test (3%)
- B. Dexamethasone suppression test (2%)
- C. Fasting plasma glucose level (0%)
- D. Serum iron studies (0%)
- E. Serum triiodothyronine and thyroxine levels (16%)
- ✓ F. Serum TSH level (75%)

Omitted
Correct answer
F

75%
Answered correctly

02 secs
Time Spent

03/31/2020
Last Updated

Explanation

This patient's symptoms (eg, fatigue, weight gain, constipation) and examination findings suggest **hypothyroidism**. Vital signs typically show bradycardia and hypertension (due to increased vascular resistance). Hypothyroidism can also cause slowed hair growth and alterations in hair growth cycles, leading to thinning of the scalp hair and lateral eyebrows. Slowed reuptake of calcium by the sarcoplasmic reticulum manifests as

This patient's symptoms (eg, fatigue, weight gain, constipation) and examination findings suggest **hypothyroidism**. Vital signs typically show bradycardia and hypertension (due to increased vascular resistance). Hypothyroidism can also cause slowed hair growth and alterations in hair growth cycles, leading to thinning of the scalp hair and lateral eyebrows. Slowed reuptake of calcium by the sarcoplasmic reticulum manifests as a delayed relaxation phase of deep tendon reflexes.

Most patients with hypothyroidism have **primary hypothyroidism** (ie, dysfunction within the thyroid gland). The thyroid releases thyroid hormones (triiodothyronine [T3] and thyroxine [T4]) in response to TSH from the pituitary. In turn, TSH secretion is regulated by thyrotropin-releasing hormone (TRH) from the hypothalamus. Thyroid hormone suppresses TSH and TRH via negative feedback, and **small changes in thyroid hormone** levels lead to **large changes in TSH** levels. As thyroid hormone production slows, TSH secretion increases rapidly to restore thyroid activity, often before T4 levels fall below standard laboratory reference ranges. Therefore, **serum TSH** is the **most sensitive** marker for primary hypothyroidism.

(Choices A and B) The 24-hour urinary cortisol assay and the dexamethasone suppression test are used to screen for Cushing syndrome. Although this patient is hypertensive, she does not have other Cushingoid features (eg, central obesity, skin striae, proximal muscle weakness).

(Choice C) Initial tests for diabetes mellitus include fasting glucose, hemoglobin A1c, and oral glucose tolerance tests. Diabetes can cause peripheral neuropathy (eg, paresthesias, loss of distal sensation, decreased ankle reflexes), but bradycardia, diastolic hypertension, and delayed relaxation of reflexes are more suggestive of hypothyroidism.

(Choice D) The initial evaluation of hereditary hemochromatosis includes serum iron studies (eg, serum iron, ferritin, transferrin saturation). Although pituitary dysfunction with secondary (central) hypothyroidism can occur, patients commonly also have arthritis, diabetes mellitus, abnormal skin pigmentation, and hepatomegaly.

(Choice E) TSH is more sensitive than either T3 or T4 for diagnosing primary hypothyroidism. TSH is not elevated in pituitary or hypothalamic disease (ie, secondary hypothyroidism), but this is a much less common cause of hypothyroidism (<5% of cases). In addition, patients with secondary hypothyroidism usually have other clinical features of hypothalamic or pituitary dysfunction.

Educational objective:
The thyroid releases thyroid hormone (triiodothyronine [T3] and thyroxine [T4]) in response to TSH from the pituitary, which is regulated by thyrotropin-releasing hormone (TRH) from the hypothalamus. Thyroid hormone suppresses the secretion of TSH and TRH via negative feedback, and small changes in thyroid hormone levels cause large changes in TSH. Serum TSH is the most sensitive test for primary hypothyroidism.

thyroid activity, often before T4 levels fall below standard laboratory reference ranges. Therefore, **serum TSH** is the **most sensitive** marker for primary hypothyroidism.

(Choices A and B) The 24-hour urinary cortisol assay and the dexamethasone suppression test are used to screen for Cushing syndrome. Although this patient is hypertensive, she does not have other Cushingoid features (eg, central obesity, skin striae, proximal muscle weakness).

(Choice C) Initial tests for diabetes mellitus include fasting glucose, hemoglobin A1c, and oral glucose tolerance tests. Diabetes can cause peripheral neuropathy (eg, paresthesias, loss of distal sensation, decreased ankle reflexes), but bradycardia, diastolic hypertension, and delayed relaxation of reflexes are more suggestive of hypothyroidism.

(Choice D) The initial evaluation of hereditary hemochromatosis includes serum iron studies (eg, serum iron, ferritin, transferrin saturation). Although pituitary dysfunction with secondary (central) hypothyroidism can occur, patients commonly also have arthritis, diabetes mellitus, abnormal skin pigmentation, and hepatomegaly.

(Choice E) TSH is more sensitive than either T3 or T4 for diagnosing primary hypothyroidism. TSH is not elevated in pituitary or hypothalamic disease (ie, secondary hypothyroidism), but this is a much less common cause of hypothyroidism (<5% of cases). In addition, patients with secondary hypothyroidism usually have other clinical features of hypothalamic or pituitary dysfunction.

Educational objective:
The thyroid releases thyroid hormone (triiodothyronine [T3] and thyroxine [T4]) in response to TSH from the pituitary, which is regulated by thyrotropin-releasing hormone (TRH) from the hypothalamus. Thyroid hormone suppresses the secretion of TSH and TRH via negative feedback, and small changes in thyroid hormone levels cause large changes in TSH. Serum TSH is the most sensitive test for primary hypothyroidism.

References

- Clinical practice guidelines for hypothyroidism in adults: cosponsored by the American Association of Clinical Endocrinologists and the American Thyroid Association.

Pathophysiology	Endocrine, Diabetes & Metabolism	Hypothyroidism
Subject	System	Topic

Copyright © UWorld. All rights reserved.

A 1-week-old boy is brought to the emergency department with recurrent vomiting and poor feeding. The infant was born full term without any complications. Physical examination shows that he is dehydrated and hypotensive.

Laboratory results are as follows:

Serum chemistry	
Sodium	122 mEq/L
Potassium	5.7 mEq/L
Blood urea nitrogen	25 mg/dL
Creatinine	0.6 mg/dL

Further evaluation will most likely show which of the following?

	Cortisol	Aldosterone	Serum ACTH	17-hydroxyprogesterone
A.	↓	↓	↑	↑
B.	↓	↑	↑	↓
C.	↓	↓	↑	↓
D.	↓	↓	↓	↑
E.	↑	↓	↑	↓

Submit

A 1-week-old boy is brought to the emergency department with recurrent vomiting and poor feeding. The infant was born full term without any complications. Physical examination shows that he is dehydrated and hypotensive.

Laboratory results are as follows:

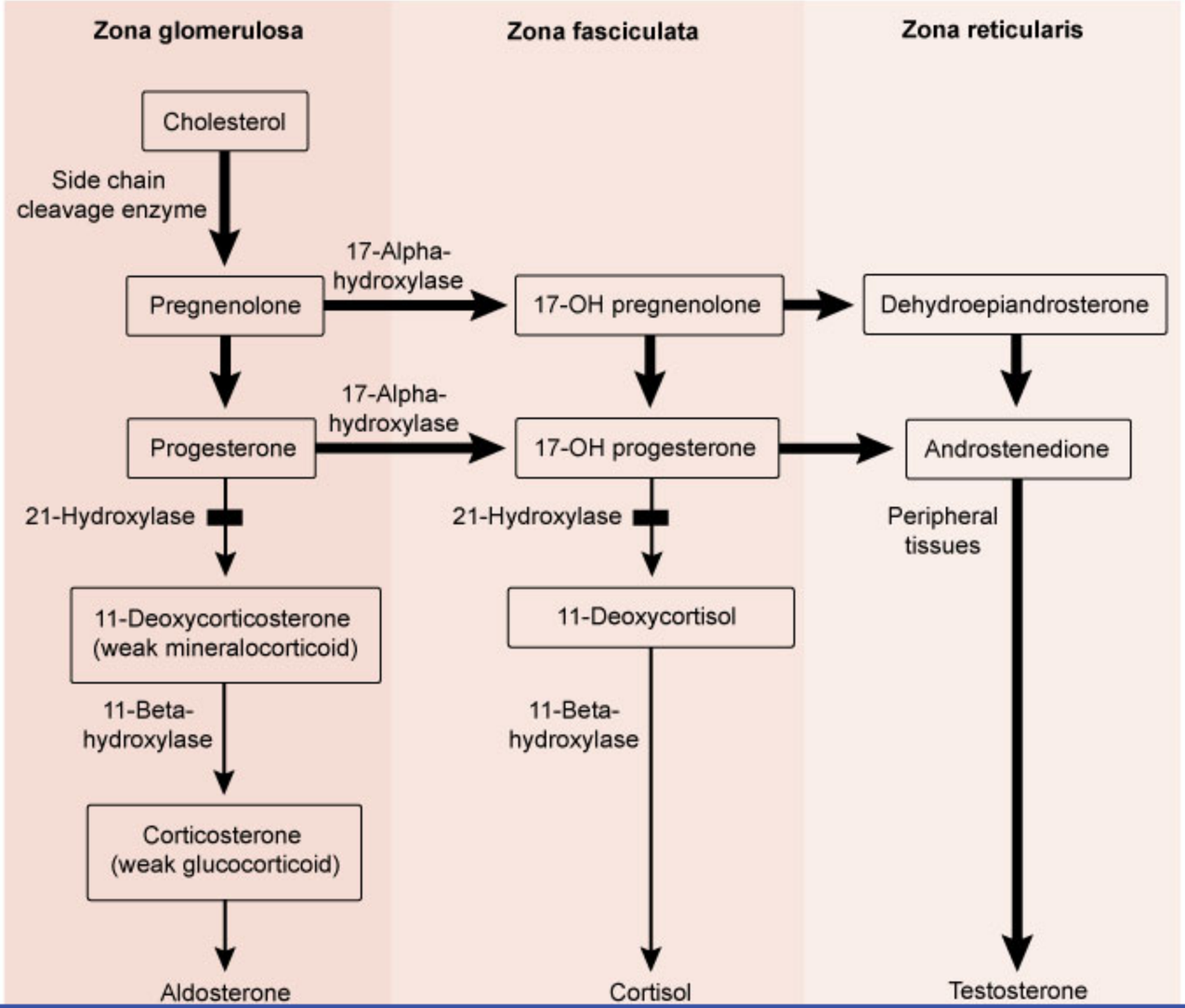
Serum chemistry	
Sodium	122 mEq/L
Potassium	5.7 mEq/L
Blood urea nitrogen	25 mg/dL
Creatinine	0.6 mg/dL

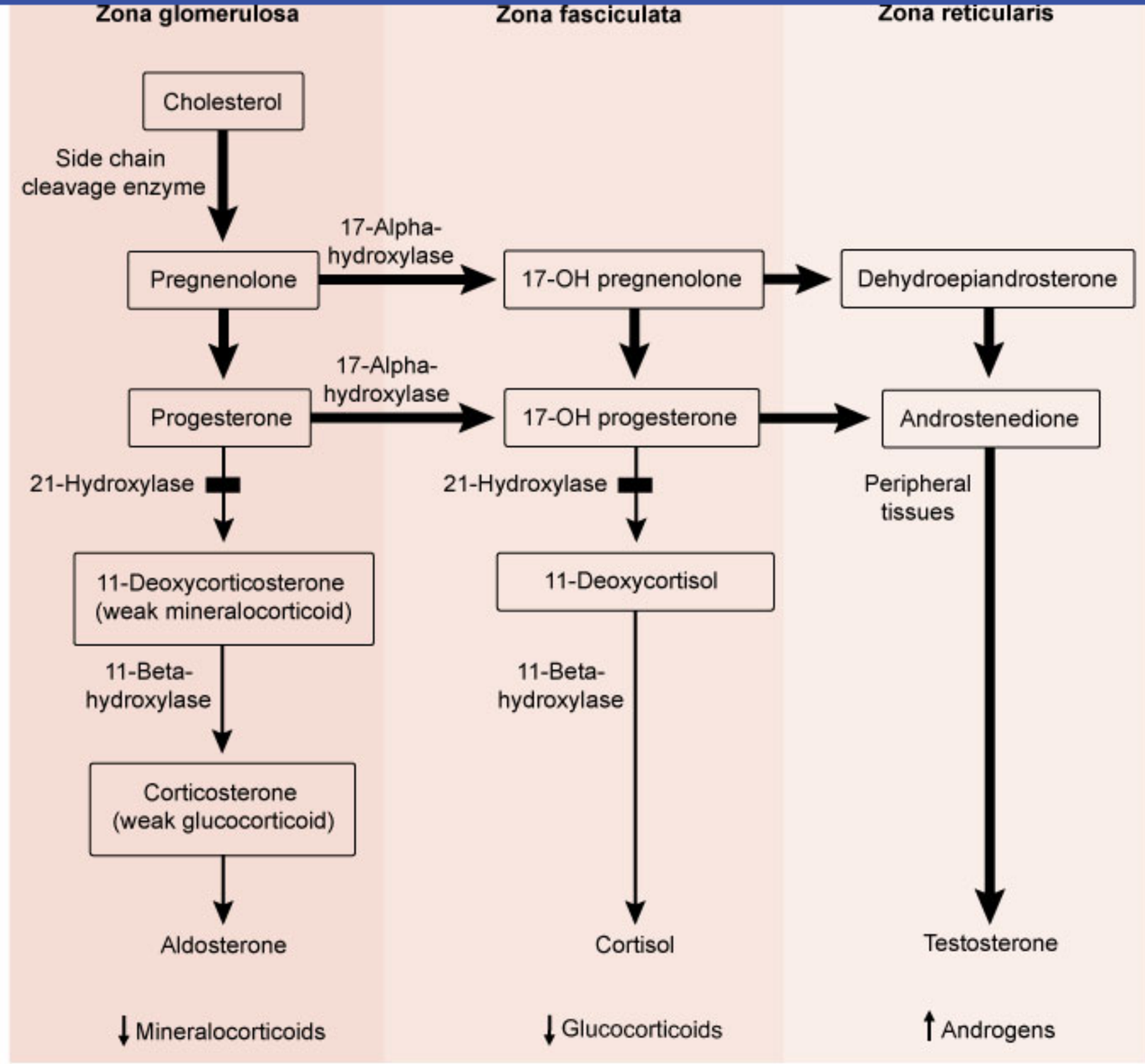
Further evaluation will most likely show which of the following?

	Cortisol	Aldosterone	Serum ACTH	17-hydroxyprogesterone
✓ A. (69%)	↓	↓	↑	↑
B. (6%)	↓	↑	↑	↓
C. (15%)	↓	↓	↑	↓
D. (3%)	↓	↓	↓	↑
E. (4%)	↑	↓	↑	↓

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31

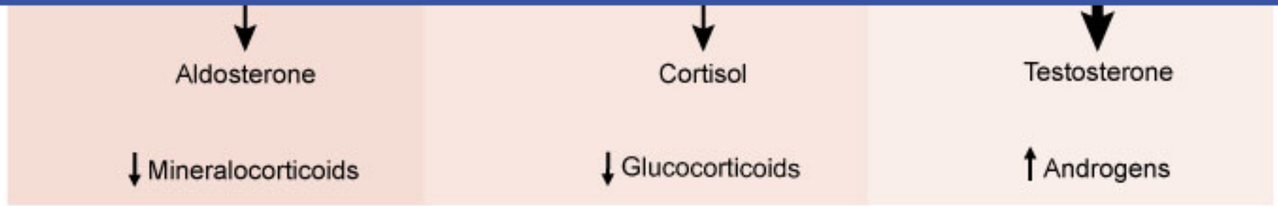
21-Hydroxylase deficiency




Zona glomerulosa
Zona fasciculata
Zona reticularis
Cholesterol
Side chain cleavage enzyme
Pregnenolone
17-Alpha-hydroxylase
17-OH pregnenolone
Dehydroepiandrosterone
Progesterone
17-Alpha-hydroxylase
17-OH progesterone
Androstenedione
21-Hydroxylase
21-Hydroxylase
Peripheral tissues
11-Deoxycorticosterone (weak mineralocorticoid)
11-Deoxycortisol
11-Beta-hydroxylase
11-Beta-hydroxylase
Corticosterone (weak glucocorticoid)
Aldosterone
Cortisol
Testosterone
Mineralocorticoids
Glucocorticoids
Androgens

©UWorld

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31



©UWorld

Congenital adrenal hyperplasia (CAH) refers to a group of autosomal recessive disorders that result from defects in the enzymes involved in cortisol biosynthesis. Deficiency of 21-hydroxylase is the most common cause of CAH, accounting for 90% of all cases.

In 21-hydroxylase deficiency, the adrenal gland cannot synthesize aldosterone and cortisol efficiently. This causes increased production of adrenal androgens because the accumulating cortisol and aldosterone precursors are diverted toward adrenal androgen biosynthesis. The resulting low cortisol levels stimulate pituitary production of ACTH, which further increases the production of adrenal androgens. 21-hydroxylase deficiency also causes increased serum levels of 17-hydroxyprogesterone as its conversion to 11-deoxycortisol is impaired by the enzymatic defect.

Increased androgen levels lead to ambiguous genitalia in females **(virilization)**, but males will have normal genitalia. **Salt-wasting** occurs with more severe enzymatic deficiencies due to lack of sufficient amounts of mineralocorticoids and presents with vomiting, hypotension, hyponatremia, and hyperkalemia. Severe enzymatic defects can also result in significant cortisol deficiency, which can cause hypoglycemia and further impair blood pressure maintenance (leading to circulatory collapse).

Educational objective:
Patients with classic, salt-wasting 21-hydroxylase deficiency have deficient cortisol and aldosterone synthesis combined with adrenal androgen overproduction. Male infants have normal genitalia and present 1-2 weeks after birth with vomiting, hypotension, hyponatremia, and hyperkalemia. Females present at birth with ambiguous genitalia.

Pathophysiology	Endocrine, Diabetes & Metabolism	Congenital adrenal hyperplasia
Subject	System	Topic

Copyright © UWorld. All rights reserved.

Exhibit Display

Enzyme deficiency	Hormonal abnormalities	Symptoms
21-hydroxylase	• ↓Cortisol & aldosterone • ↑Testosterone • ↑17-hydroxyprogesterone	• Ambiguous genitalia in girls • Salt wasting (vomiting, hypotension, ↓Na^+, ↑K^+)
11β-hydroxylase	• ↓Cortisol & aldosterone • ↑Testosterone • ↑11-deoxycorticosterone (weak mineralocorticoid) & 11- deoxycortisol	• Ambiguous genitalia in girls • Fluid & salt retention, hypertension
17α-hydroxylase	• ↓Cortisol & testosterone • ↑Mineralocorticoids • ↑Corticosterone (weak glucocorticoid)	• All patients phenotypically female • Fluid & salt retention, hypertension

©UWorld

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31

A 43-year-old woman comes to the office to discuss amenorrhea. She began having irregular menses 2 years ago, and her last menstrual period was 9 months ago. Family history is unremarkable. Laboratory studies show an increased serum prolactin level, a normal TSH level, and an undetectable β-hCG concentration. Serum calcium is normal. MRI reveals a 6-mm pituitary adenoma. The patient refuses medical and surgical therapy as she is happy about not having menstrual periods. If left untreated, this patient is at greatest risk of developing which of the following?

A. Cortical stroke

B. Gastric ulcer

C. Loss of bone mass

D. Myocardial infarction

E. Secondary diabetes mellitus

Submit

A 43-year-old woman comes to the office to discuss amenorrhea. She began having irregular menses 2 years ago, and her last menstrual period was 9 months ago. Family history is unremarkable. Laboratory studies show an increased serum prolactin level, a normal TSH level, and an undetectable β-hCG concentration. Serum calcium is normal. MRI reveals a 6-mm pituitary adenoma. The patient refuses medical and surgical therapy as she is happy about not having menstrual periods. If left untreated, this patient is at greatest risk of developing which of the following?

- A. Cortical stroke (12%)
- B. Gastric ulcer (2%)
- ✓ C. Loss of bone mass (75%)
- D. Myocardial infarction (2%)
- E. Secondary diabetes mellitus (7%)

Omitted
Correct answer
C

75%
Answered correctly

02 secs
Time Spent

02/15/2020
Last Updated

Explanation

Prolactinoma	
Clinical features	• **Premenopausal women**: Oligomenorrhea/amenorrhea, infertility, galactorrhea, hot flashes, decreased bone density • **Postmenopausal women**: Mass-effect symptoms (headache, visual field defects) • **Men**: Infertility, decreased libido, impotence, gynecomastia

Prolactinoma	
Clinical features	• **Premenopausal women**: Oligomenorrhea/amenorrhea, infertility, galactorrhea, hot flashes, decreased bone density • **Postmenopausal women**: Mass-effect symptoms (headache, visual field defects) • **Men**: Infertility, decreased libido, impotence, gynecomastia
Laboratory/ imaging	• Serum prolactin (often >200 ng/mL) • Tests to rule out renal insufficiency (creatinine) & hypothyroidism (TSH, thyroxine) • MRI of the brain/pituitary
Treatment	• Dopamine agonist (cabergoline) • Trans-sphenoidal surgery

This patient's small **pituitary adenoma** with an **elevated prolactin** level and **secondary amenorrhea** is consistent with a prolactin-secreting adenoma **(prolactinoma)**. High levels of prolactin suppress GnRH secretion from the hypothalamus, leading to reduced secretion of LH (and to a lesser extent FSH) and subsequent **hypogonadism**. Nonsecretory ("nonfunctioning") adenomas can also cause mild hyperprolactinemia due to pressure on the stalk, but these tumors primarily cause mass-effect symptoms (eg, hypopituitarism, headache, bitemporal hemianopsia) due to pressure on surrounding structures.

Estrogen maintains bone mass in premenopausal women. Low estrogen levels lead to increased production of inflammatory cytokines (especially IL-1 and tumor necrosis factor–alpha), increasing expression of the receptor activator of nuclear factor kappa B ligand (RANKL) and resulting in increased osteoclast activity. Loss of estrogen, whether from menopause, ovulatory dysfunction, or surgical removal of the ovaries, increases the risk of bone loss and **osteoporosis**.

(Choice A) Adenomas are associated with pituitary apoplexy (hemorrhage into the pituitary). However, this occurs more commonly with large adenomas and is not typically associated with strokes located in the cortex.

(Choice B) Multiple endocrine neoplasia (MEN) type 1 is characterized by pituitary adenomas, hyperparathyroidism, and endocrine tumors of the pancreas. Gastrin-secreting pancreatic tumors are common and may lead to recurrent peptic ulcers (Zollinger-Ellison syndrome). However,

1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25 26 27 28 29 30 31

- Trans-sphenoidal surgery

This patient's small **pituitary adenoma** with an **elevated prolactin** level and **secondary amenorrhea** is consistent with a prolactin-secreting adenoma **(prolactinoma)**. High levels of prolactin suppress GnRH secretion from the hypothalamus, leading to reduced secretion of LH (and to a lesser extent FSH) and subsequent **hypogonadism**. Nonsecretory ("nonfunctioning") adenomas can also cause mild hyperprolactinemia due to pressure on the stalk, but these tumors primarily cause mass-effect symptoms (eg, hypopituitarism, headache, bitemporal hemianopsia) due to pressure on surrounding structures.

Estrogen maintains bone mass in premenopausal women. Low estrogen levels lead to increased production of inflammatory cytokines (especially IL-1 and tumor necrosis factor–alpha), increasing expression of the receptor activator of nuclear factor kappa B ligand (RANKL) and resulting in increased osteoclast activity. Loss of estrogen, whether from menopause, ovulatory dysfunction, or surgical removal of the ovaries, increases the risk of bone loss and **osteoporosis**.

(Choice A) Adenomas are associated with pituitary apoplexy (hemorrhage into the pituitary). However, this occurs more commonly with large adenomas and is not typically associated with strokes located in the cortex.

(Choice B) Multiple endocrine neoplasia (MEN) type 1 is characterized by pituitary adenomas, hyperparathyroidism, and endocrine tumors of the pancreas. Gastrin-secreting pancreatic tumors are common and may lead to recurrent peptic ulcers (Zollinger-Ellison syndrome). However, almost all patients with MEN type 1 have hyperparathyroidism with hypercalcemia.

(Choice D) Early menopause (age <40) is associated with an increased risk of cardiovascular events, but the effect of the prolactinoma-induced low estrogenic state on cardiovascular risk in older women is unclear.

(Choice E) Excess growth hormone secretion from a somatotroph pituitary adenoma can lead to diabetes mellitus due to increased insulin resistance in peripheral tissues. However, adults typically present with acromegaly.

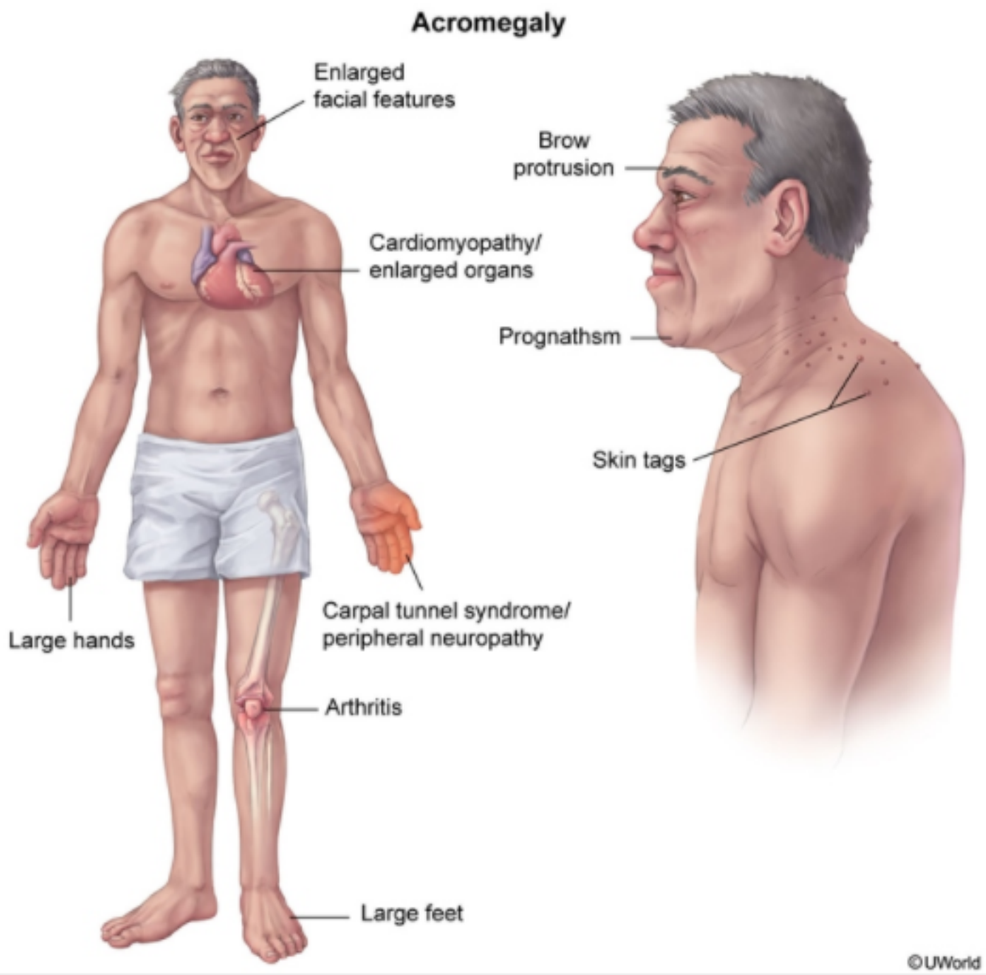
Educational objective:
Hyperprolactinemia suppresses secretion of GnRH, which leads to reduced estrogen in women. Low estrogen levels are a risk factor for accelerated bone loss.

References

- The risk of osteopenia in premenopausal women with various sellar tumors.

This patient's small **pituitary adenoma** with an **elevated prolactin** level and **secondary amenorrhea** is consistent with a prolactin-secreting adenoma (**prolactinoma**). High levels of prolactin suppress GnRH secretion from the hypothalamus, leading to reduced secretion of LH (and to a

Exhibit Display

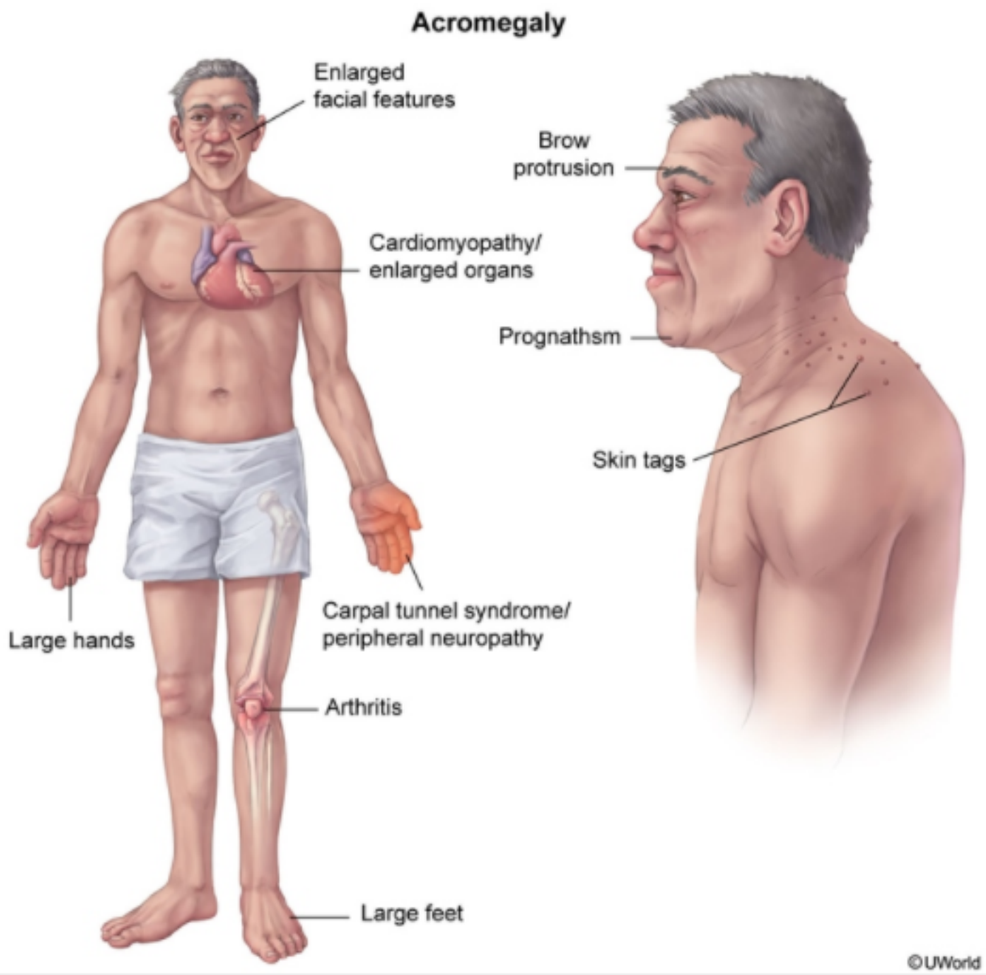


Zoom In | Zoom Out | Reset | Add To New Card | Existing Card

Pathophysiology | Endocrine, Diabetes & Metabolism | Pituitary adenoma

This patient's small **pituitary adenoma** with an **elevated prolactin** level and **secondary amenorrhea** is consistent with a prolactin-secreting adenoma (**prolactinoma**). High levels of prolactin suppress GnRH secretion from the hypothalamus, leading to reduced secretion of LH (and to a

Exhibit Display



Zoom In | Zoom Out | Reset | Add To New Card | Existing Card

Pathophysiology | Endocrine, Diabetes & Metabolism | Pituitary adenoma

pressure on surrounding structures.

Estrogen maintains bone mass in premenopausal women. Low estrogen levels lead to increased production of inflammatory cytokines (especially IL-1 and tumor necrosis factor–alpha), increasing expression of the receptor activator of nuclear factor kappa B ligand (RANKL) and resulting in increased osteoclast activity. Loss of estrogen, whether from menopause, ovulatory dysfunction, or surgical removal of the ovaries, increases the risk of bone loss and **osteoporosis**.

(Choice A) Adenomas are associated with pituitary apoplexy (hemorrhage into the pituitary). However, this occurs more commonly with large adenomas and is not typically associated with strokes located in the cortex.

(Choice B) Multiple endocrine neoplasia (MEN) type 1 is characterized by pituitary adenomas, hyperparathyroidism, and endocrine tumors of the pancreas. Gastrin-secreting pancreatic tumors are common and may lead to recurrent peptic ulcers (Zollinger-Ellison syndrome). However, almost all patients with MEN type 1 have hyperparathyroidism with hypercalcemia.

(Choice D) Early menopause (age <40) is associated with an increased risk of cardiovascular events, but the effect of the prolactinoma-induced low estrogenic state on cardiovascular risk in older women is unclear.

(Choice E) Excess growth hormone secretion from a somatotroph pituitary adenoma can lead to diabetes mellitus due to increased insulin resistance in peripheral tissues. However, adults typically present with acromegaly.

Educational objective:
Hyperprolactinemia suppresses secretion of GnRH, which leads to reduced estrogen in women. Low estrogen levels are a risk factor for accelerated bone loss.

References

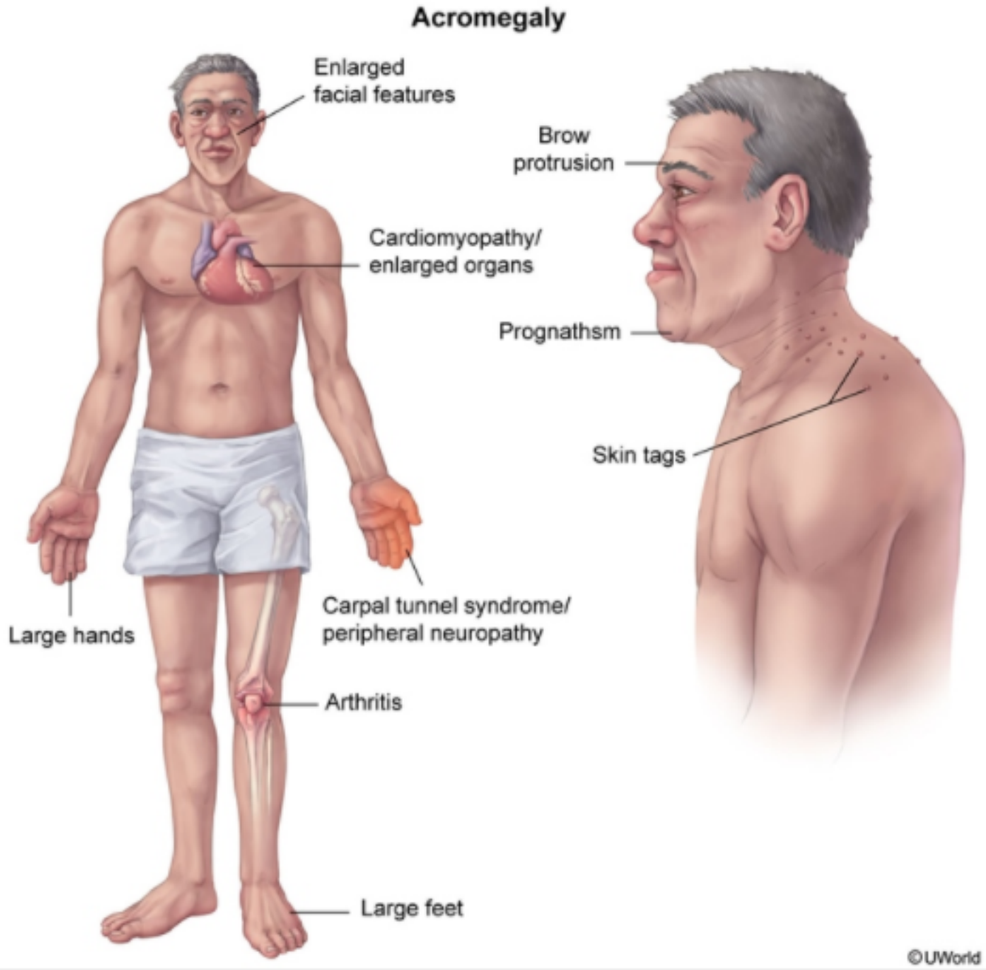
- The risk of osteopenia in premenopausal women with various sellar tumors.

Pathophysiology	Endocrine, Diabetes & Metabolism	Pituitary adenoma
Subject	System	Topic

Copyright © UWorld. All rights reserved.

pressure on surrounding structures

Exhibit Display



Zoom In | Zoom Out | Reset | Add To New Card | Existing Card

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31

A 16-year-old girl is brought to the office by her mother due to concern about excessive weight loss. The patient has lost 4.5 kg (10 lb) over the past 2 months, but thinks she still appears overweight, and is worried about gaining weight. She does not use tobacco, alcohol, or illicit drugs. Her mother has hypothyroidism. Blood pressure is 130/70 mm Hg, and pulse is 105/min and regular. There are no orthostatic changes. BMI is 22 kg/m^2. On examination, the patient appears anxious. The thyroid is small and without palpable nodules. There is a fine tremor of outstretched hands. Deep tendon reflexes are 3+ diffusely. The skin is warm and moist. Laboratory results show decreased TSH, elevated free thyroxine (T4), and undetectable thyroglobulin levels. Which of the following is most likely to be seen on thyroid biopsy of this patient?

A. Diffuse atrophy of the thyroid follicles with decreased colloid

B. Extensive lymphocytic infiltrate with germinal center formation

C. Inflammatory disruption of the follicles and multinucleated giant cells

D. Small clusters of spindle cells and foci of C-cell hyperplasia

E. Tall columnar follicular epithelium with scalloped margins of the colloid

Submit

A 16-year-old girl is brought to the office by her mother due to concern about excessive weight loss. The patient has lost 4.5 kg (10 lb) over the past 2 months, but thinks she still appears overweight, and is worried about gaining weight. She does not use tobacco, alcohol, or illicit drugs. Her mother has hypothyroidism. Blood pressure is 130/70 mm Hg, and pulse is 105/min and regular. There are no orthostatic changes. BMI is 22 kg/m^2. On examination, the patient appears anxious. The thyroid is small and without palpable nodules. There is a fine tremor of outstretched hands. Deep tendon reflexes are 3+ diffusely. The skin is warm and moist. Laboratory results show decreased TSH, elevated free thyroxine (T4), and undetectable thyroglobulin levels. Which of the following is most likely to be seen on thyroid biopsy of this patient?

- ✓ A. Diffuse atrophy of the thyroid follicles with decreased colloid (43%)
- B. Extensive lymphocytic infiltrate with germinal center formation (12%)
- C. Inflammatory disruption of the follicles and multinucleated giant cells (4%)
- D. Small clusters of spindle cells and foci of C-cell hyperplasia (2%)
- E. Tall columnar follicular epithelium with scalloped margins of the colloid (36%)

Omitted
Correct answer
A

43%
Answered correctly

03 secs
Time Spent

04/25/2020
Last Updated

Explanation

This patient's symptoms (eg, weight loss, tachycardia, and tremors), elevated free thyroxine (T4), and suppressed TSH are indicative of **thyrotoxicosis**. However, her thyroid is small and serum **thyroglobulin is undetectable**, which suggests an **exogenous source** of thyroid hormone. Thyroglobulin is a glycoprotein produced by thyroid follicular cells that makes up a substantial component of follicular colloid and serves as the substrate for the formation of thyroid hormone. A small amount is released by the thyroid in normal function. Low levels, as in this patient,

This patient's symptoms (eg, weight loss, tachycardia, and tremors), elevated free thyroxine (T4), and suppressed TSH are indicative of **thyrotoxicosis**. However, her thyroid is small and serum **thyroglobulin is undetectable**, which suggests an **exogenous source** of thyroid hormone. Thyroglobulin is a glycoprotein produced by thyroid follicular cells that makes up a substantial component of follicular colloid and serves as the substrate for the formation of thyroid hormone. A small amount is released by the thyroid in normal function. Low levels, as in this patient, suggest noninflammatory **suppression of thyroid activity**.

In light of her mother's hypothyroidism, which suggests a possible source of levothyroxine tablets, this patient is likely surreptitiously taking thyroid hormone, possibly in an attempt to lose weight or have increased energy. Exogenous thyrotoxicosis can also occur in patients taking over-the-counter supplements containing animal thyroid tissue and in erroneous dosing of thyroid replacement therapy. Excess T4 supplementation suppresses TSH, which decreases iodine organification and colloid formation resulting in **atrophy of thyroid follicles**.

(Choice B) Histopathology in chronic autoimmune (Hashimoto) thyroiditis is characterized by a mononuclear infiltrate consisting of lymphocytes and plasma cells, often with germinal centers. Hashimoto thyroiditis typically presents with primary hypothyroidism (elevated TSH, low free T4) and goiter.

(Choice C) Subacute granulomatous (de Quervain) thyroiditis is characterized by disruption of follicles and a mixed cellular infiltrate with occasional multinucleated giant cells. Patients may have hyperthyroidism but typically have a painful, tender thyroid gland and high levels of thyroglobulin due to destructive thyroiditis.

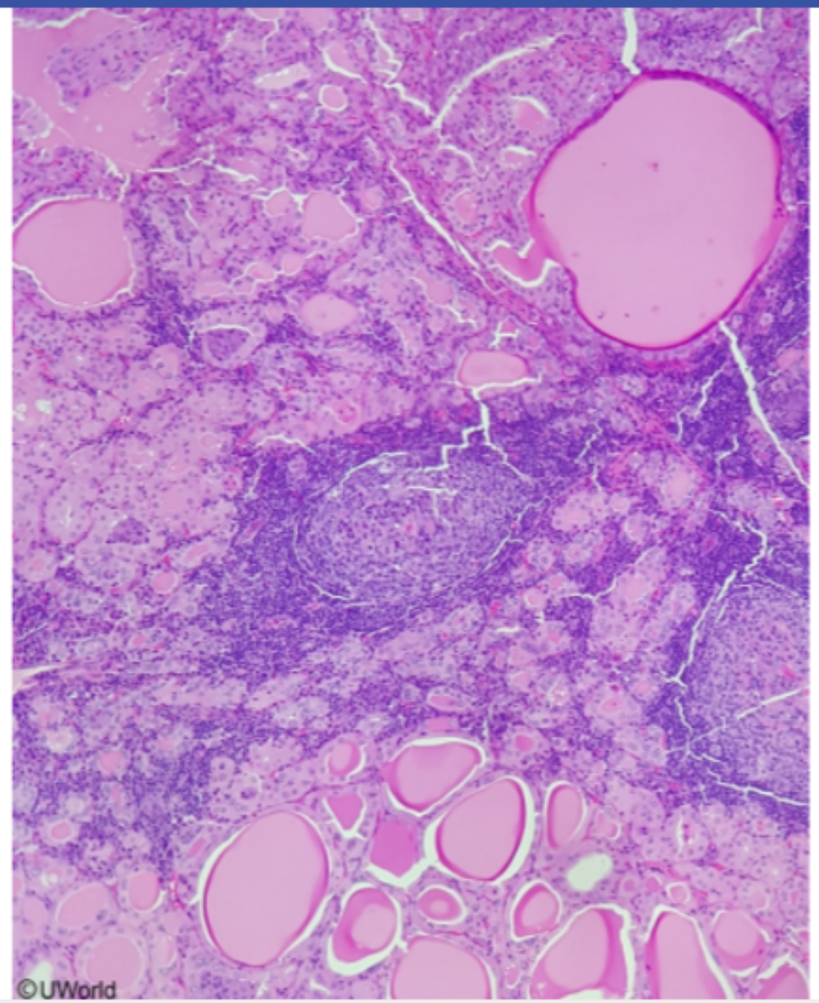
(Choice D) Medullary thyroid cancer is a neuroendocrine tumor that arises from calcitonin-secreting parafollicular C cells. Microscopy shows nests or sheets of polygonal or spindle-shaped cells with extracellular amyloid deposits (derived from calcitonin). Clinical features include diarrhea, flushing, and thyroid nodules, but TSH and free T4 are normal.

(Choice E) Graves disease presents with a diffusely enlarged thyroid gland associated with hyperthyroidism, exophthalmos, and pretibial myxedema. The thyroid follicular epithelium is tall and crowded with hyperactive reabsorption, causing scalloping around the edges of the colloid. However, high serum levels of thyroglobulin would be seen due to increased thyroid metabolic activity.

Educational objective:
Exogenous hyperthyroidism is characterized by elevated free thyroxine (T4), suppressed TSH, and low/undetectable thyroglobulin. It can occur with surreptitious levothyroxine abuse, use of animal-sourced thyroid supplements, and erroneous dosing of thyroid replacement therapy. Over

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31

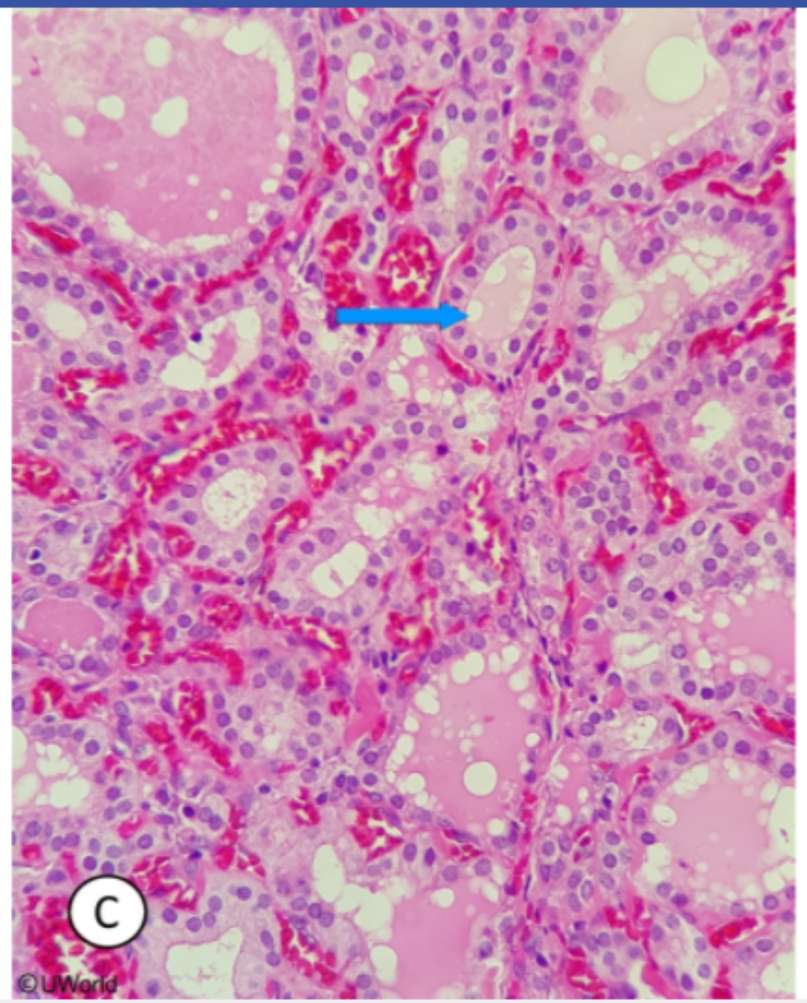
Exhibit Display



Zoom In
Zoom Out
Reset
Add To New Card | Existing Card

counter supplements containing animal thyroid tissue and in erroneous dosing of thyroid replacement therapy. Excess T4 supplementation

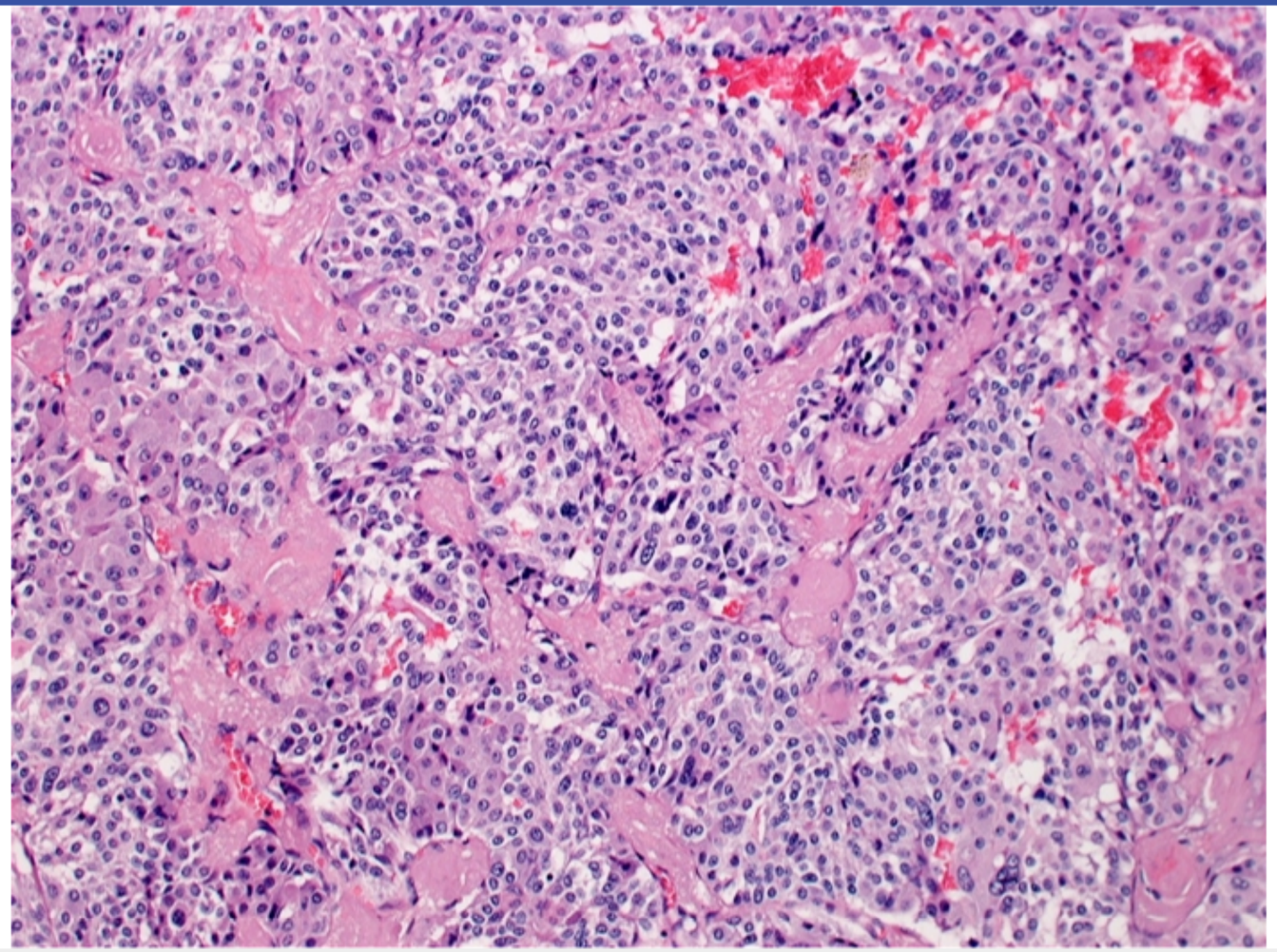
Exhibit Display



Zoom In | Zoom Out | Reset | Add To New Card | Existing Card

counter supplements containing animal thyroid tissue and in erroneous dosing of thyroid replacement therapy. Excess T4 supplementation

Exhibit Display



Zoom In | Zoom Out | Reset | Add To New Card | Existing Card

A 34-year-old woman experiences nausea, abdominal pain, and dizziness after undergoing open reduction and internal fixation of a femur fracture. One year ago, she was diagnosed with systemic lupus erythematosus with significant renal involvement, and she has since been on chronic glucocorticoid therapy with prednisone. The patient was maintained on her usual daily dose of prednisone throughout the perioperative period. Blood pressure is 90/60 mm Hg and pulse is 120/min. Compared to the normal physiologic response to surgery, this patient most likely has which of the following patterns of hypothalamic-pituitary-adrenal axis activity?

	Corticotropin-releasing hormone	ACTH	Cortisol
A.	Increased	Increased	Increased
B.	Increased	Increased	Decreased
C.	Increased	Decreased	Decreased
D.	Decreased	Decreased	Increased
E.	Decreased	Decreased	Decreased

Submit

A 34-year-old woman experiences nausea, abdominal pain, and dizziness after undergoing open reduction and internal fixation of a femur fracture. One year ago, she was diagnosed with systemic lupus erythematosus with significant renal involvement, and she has since been on chronic glucocorticoid therapy with prednisone. The patient was maintained on her usual daily dose of prednisone throughout the perioperative period. Blood pressure is 90/60 mm Hg and pulse is 120/min. Compared to the normal physiologic response to surgery, this patient most likely has which of the following patterns of hypothalamic-pituitary-adrenal axis activity?

	Corticotropin-releasing hormone	ACTH	Cortisol
A. (1%)	Increased	Increased	Increased
B. (12%)	Increased	Increased	Decreased
C. (6%)	Increased	Decreased	Decreased
D. (22%)	Decreased	Decreased	Increased
✓ E. (56%)	Decreased	Decreased	Decreased

Omitted
Correct answer
E

56%
Answered correctly

03 secs
Time Spent

01/16/2020
Last Updated

Explanation

This patient is suffering from **acute adrenal insufficiency (adrenal crisis)** due to suppression of the hypothalamic-pituitary-adrenal (HPA) axis by long-term glucocorticoid therapy. Glucocorticoids suppress the synthesis and release of corticotropin-releasing hormone (CRH) from the hypothalamus and also block its ACTH stimulatory effect on the anterior pituitary. Long-term suppression leads to **atrophy** of hypothalamic CRH-releasing neurons, pituitary corticotrophic cells, and the adrenal zona reticularis (androgen- producing inner zone) and zona fasciculata (cortisol-producing middle zone).

Chronic glucocorticoid use is characterized by **low** CRH, ACTH, and cortisol levels that **cannot rise** in response to stressful situations (eg, infections, surgery) **(Choice A)**. This lack of a stress response can result in **relative glucocorticoid deficiency** even when the patient's baseline glucocorticoid regimen is maintained. Because glucocorticoids help maintain normal vascular tone (eg, by increasing norepinephrine, renin, and angiotensin vasoconstrictive activity), glucocorticoid deficiency can precipitate **hypotension/shock**. In such cases, a higher **stress dose** is needed to compensate for the increased physiologic demands and prevent the development of adrenal crisis.

(Choice B) Increased levels of CRH and ACTH with decreased cortisol suggest primary adrenal insufficiency, as may be seen in autoimmune adrenalitis or bilateral adrenal hemorrhage/infarction. These patients will also have mineralocorticoid deficiency and are at very high risk for adrenal crisis.

(Choice C) Increased CRH with decreased levels of ACTH and cortisol suggest a pituitary disorder. ACTH is secreted by corticotroph cells of the anterior pituitary; damage to the pituitary by a tumor, infarction, or infection can cause decreased release of ACTH, which in turn leads to decreased cortisol production.

(Choice D) Excessive cortisol production from an autonomous adrenal adenoma suppresses CRH and ACTH production by the hypothalamus and pituitary, respectively.

Educational objective:
Suppression of the hypothalamus-pituitary-adrenal axis by glucocorticoid therapy is the most common cause of adrenal insufficiency. In these patients, adrenal crisis can be precipitated by stressful situations (eg, infections, surgery) if the glucocorticoid dose is not increased appropriately.

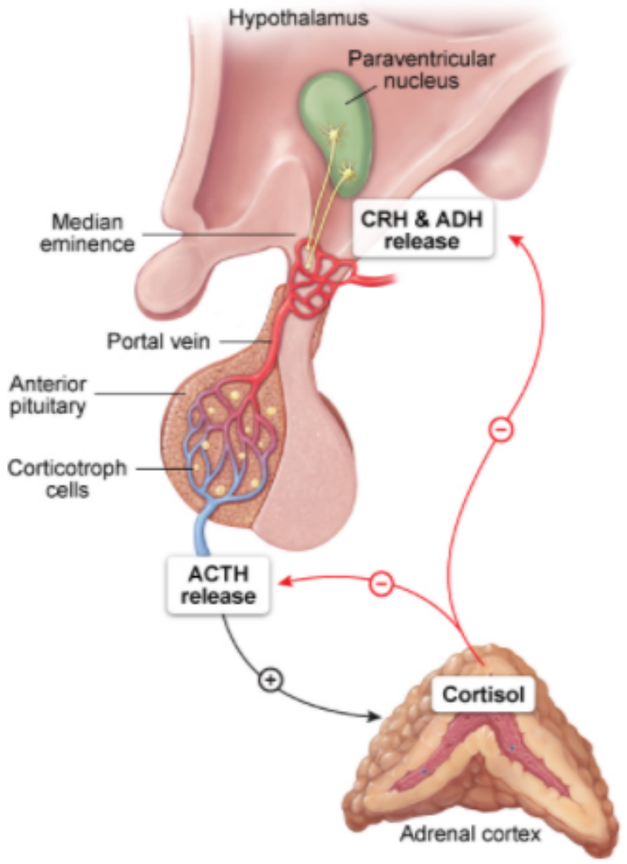
References

- Extensive expertise in endocrinology. Adrenal crisis.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31

Exhibit Display

Hypothalamic-pituitary-adrenal axis



ADH = antidiuretic hormone; CRH = corticotropin-releasing hormone.

©UWorld

Zoom In | Zoom Out | Reset | Add To New Card | Existing Card

Educational objective:

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31

A group of investigators is studying the mechanisms of signal transduction involved in the pathogenesis of type 2 diabetes mellitus. Their research focuses on the intracellular signaling cascade that begins when insulin binds to the insulin receptor. In a series of experiments, they demonstrate that pre-treatment with tumor necrosis factor alpha (TNF-α) results in decreased insulin-mediated glucose uptake. This effect of TNF-α is most likely mediated through upregulation of which of the following processes?

A. Cyclic AMP hydrolyzation

B. Phosphatidylinositol cleavage

C. Proline residue hydroxylation

D. Serine residue phosphorylation

E. Stimulation of peroxisome proliferator-activated receptor

Submit

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31

A group of investigators is studying the mechanisms of signal transduction involved in the pathogenesis of type 2 diabetes mellitus. Their research focuses on the intracellular signaling cascade that begins when insulin binds to the insulin receptor. In a series of experiments, they demonstrate that pre-treatment with tumor necrosis factor alpha (TNF-α) results in decreased insulin-mediated glucose uptake. This effect of TNF-α is most likely mediated through upregulation of which of the following processes?

A. Cyclic AMP hydrolyzation (25%)

B. Phosphatidylinositol cleavage (18%)

C. Proline residue hydroxylation (4%)

✓ D. Serine residue phosphorylation (31%)

E. Stimulation of peroxisome proliferator-activated receptor (19%)

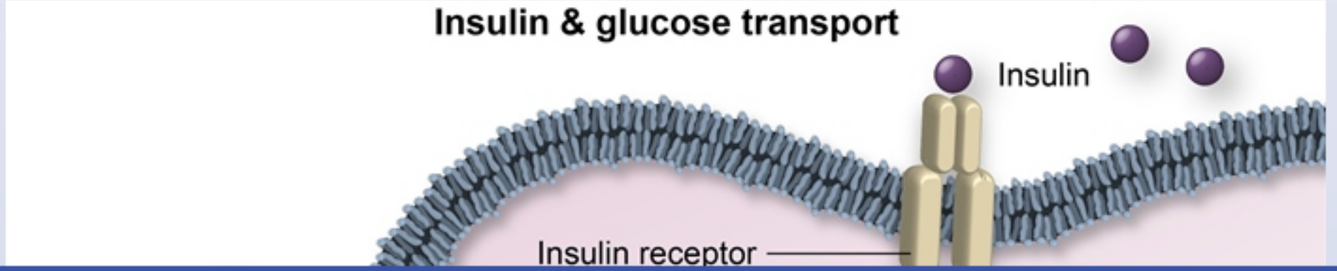
Omitted
Correct answer
D

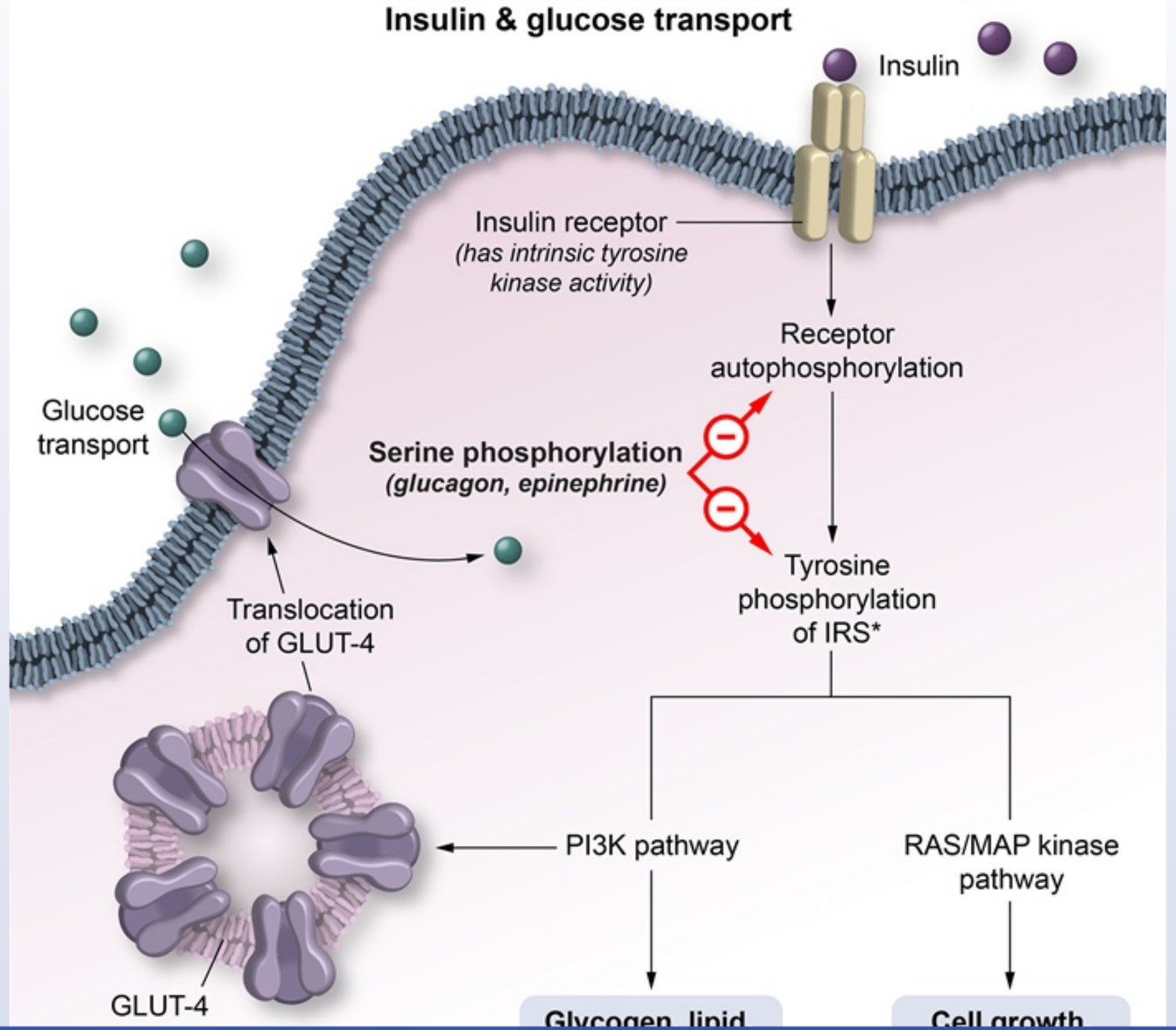
31%
Answered correctly

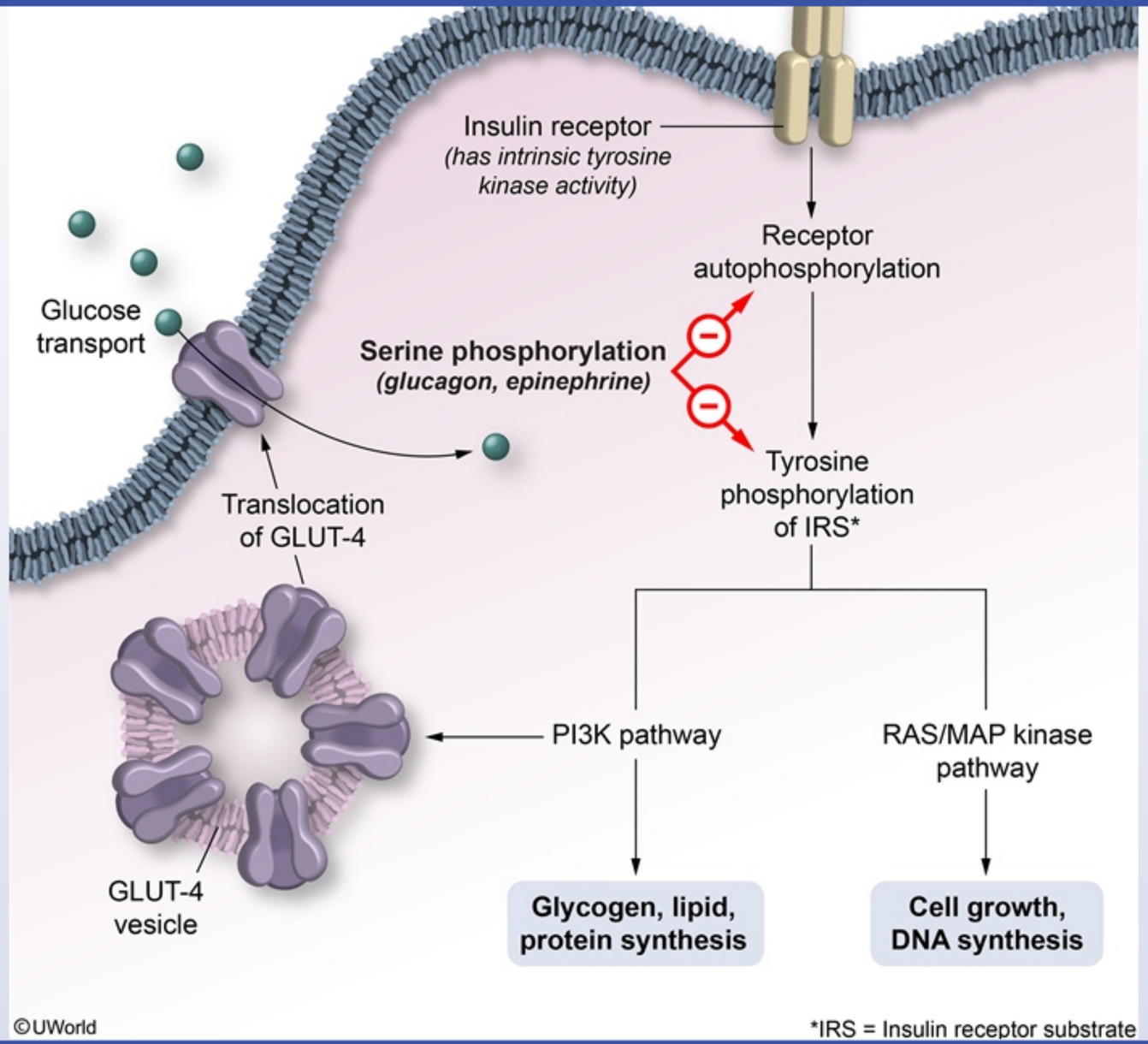
02 secs
Time Spent

03/08/2020
Last Updated

Explanation




Insulin & glucose transport
Insulin
Insulin receptor
(has intrinsic tyrosine kinase activity)
Receptor autophosphorylation
Glucose transport
Serine phosphorylation
(glucagon, epinephrine)
Tyrosine phosphorylation of IRS*
Translocation of GLUT-4
PI3K pathway
RAS/MAP kinase pathway
GLUT-4
Glycogen, lipid
Cell growth


Insulin receptor
(has intrinsic tyrosine kinase activity)
Receptor autophosphorylation
Glucose transport
Serine phosphorylation
(glucagon, epinephrine)
Tyrosine phosphorylation of IRS*
Translocation of GLUT-4
GLUT-4 vesicle
PI3K pathway
RAS/MAP kinase pathway
Glycogen, lipid, protein synthesis
Cell growth, DNA synthesis
©UWorld
*IRS = Insulin receptor substrate

The **insulin receptor** (IR) is a tetrameric structure consisting of 2 alpha and 2 beta subunits. The alpha subunits are extracellular and provide the binding site for insulin. The beta subunits are intracellular and contain **tyrosine kinase** domains that are activated when insulin attaches to the alpha subunits. A series of downstream signaling is then triggered, starting with the autophosphorylation of IR, phosphorylation of IR substrates 1 and 2 (IRS-1/2), and ultimately, translocation of glucose transporter-4 (GLUT-4) to the cell membrane.

Tumor necrosis factor alpha (TNF-α) is a proinflammatory cytokine that induces insulin resistance through the activation of **serine kinases**, which then phosphorylate serine residues on the beta subunits of IR and IRS-1. This inhibits tyrosine phosphorylation of IRS-1 by IR and subsequently hinders downstream signaling, resulting in resistance to the normal actions of insulin. Phosphorylation of threonine residues has similar effects. Catecholamines, glucocorticoids, and glucagon can also induce insulin resistance by this same mechanism.

(Choice A) Cyclic AMP (cAMP) is inactivated via hydrolysis by phosphodiesterase. Phosphodiesterase can thereby dampen the effects of various hormones (eg, glucagon) that use cAMP as a second messenger. cAMP is also involved in insulin release by pancreatic beta cells, but it does not participate in IR downstream signaling.

(Choice B) Some hormones (eg, angiotensin II, gonadotropin-releasing hormone) act on transmembrane receptors coupled with a G_q-protein that activates phospholipase C, which then cleaves phosphatidylinositol biphosphate into two important secondary messengers: inositol triphosphate and diacylglycerol (DAG). Inositol triphosphate mediates its action by increasing intracellular calcium influx, and DAG activates protein kinase C.

(Choice C) Hydroxyproline, a major component of bone and skin collagen, is formed by the hydroxylation of proline, which requires vitamin C. Insulin plays no role in the hydroxylation of proline.

(Choice E) Peroxisome proliferator-activated receptor-gamma (PPAR-γ) alters gene transcription by binding to the promoter region of target genes. Activation of PPAR-γ results in improved insulin sensitivity.

Educational objective:
Phosphorylation of serine and threonine residues of insulin receptor and insulin receptor substrate by serine kinase leads to insulin resistance. This type of phosphorylation can be induced by TNF-α, catecholamines, glucocorticoids, and glucagon.

References

- Insulin resistance induced by tumor necrosis factor-alpha in myocytes and brown adipocytes.

Tumor necrosis factor alpha (TNF-α) is a proinflammatory cytokine that induces insulin resistance through the activation of **serine kinases**, which then phosphorylate serine residues on the beta subunits of IR and IRS-1. This inhibits tyrosine phosphorylation of IRS-1 by IR and subsequently hinders downstream signaling, resulting in resistance to the normal actions of insulin. Phosphorylation of threonine residues has similar effects. Catecholamines, glucocorticoids, and glucagon can also induce insulin resistance by this same mechanism.

(Choice A) Cyclic AMP (cAMP) is inactivated via hydrolysis by phosphodiesterase. Phosphodiesterase can thereby dampen the effects of various hormones (eg, glucagon) that use cAMP as a second messenger. cAMP is also involved in insulin release by pancreatic beta cells, but it does not participate in IR downstream signaling.

(Choice B) Some hormones (eg, angiotensin II, gonadotropin-releasing hormone) act on transmembrane receptors coupled with a G_q-protein that activates phospholipase C, which then cleaves phosphatidylinositol biphosphate into two important secondary messengers: inositol triphosphate and diacylglycerol (DAG). Inositol triphosphate mediates its action by increasing intracellular calcium influx, and DAG activates protein kinase C.

(Choice C) Hydroxyproline, a major component of bone and skin collagen, is formed by the hydroxylation of proline, which requires vitamin C. Insulin plays no role in the hydroxylation of proline.

(Choice E) Peroxisome proliferator-activated receptor-gamma (PPAR-γ) alters gene transcription by binding to the promoter region of target genes. Activation of PPAR-γ results in improved insulin sensitivity.

Educational objective:
Phosphorylation of serine and threonine residues of insulin receptor and insulin receptor substrate by serine kinase leads to insulin resistance. This type of phosphorylation can be induced by TNF-α, catecholamines, glucocorticoids, and glucagon.

References

- Insulin resistance induced by tumor necrosis factor-alpha in myocytes and brown adipocytes.

Pathophysiology	Endocrine, Diabetes & Metabolism	Diabetes mellitus
Subject	System	Topic

Copyright © UWorld. All rights reserved.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31

A 45-year-old previously healthy man comes to the office due to worsening muscle pain and weakness over the past 6 months. Carrying heavy items such as groceries has become increasingly difficult, and any prolonged activity causes diffuse muscle cramps. He has also had a 4.5-kg (10-lb) weight gain over this time. The patient takes no medications and does not use tobacco, alcohol, or illicit drugs. Blood pressure is 140/90 mm Hg and pulse is 56/min. BMI is 26 kg/m^2. Physical examination shows muscle weakness, predominantly of the shoulder and hip girdles. When the knee reflex is elicited, the quadriceps muscle contracts briskly but relaxation takes longer than normal. There are splitting and peeling of the nails. Serum creatine kinase is elevated. Which of the following tests is most likely to identify the cause of this patient's muscle weakness?

A. 24-hour urinary cortisol excretion

B. Acetylcholine receptor antibody titers

C. CT scan of the chest

D. Muscle biopsy

E. Serum TSH level

Submit

A 45-year-old previously healthy man comes to the office due to worsening muscle pain and weakness over the past 6 months. Carrying heavy items such as groceries has become increasingly difficult, and any prolonged activity causes diffuse muscle cramps. He has also had a 4.5-kg (10-lb) weight gain over this time. The patient takes no medications and does not use tobacco, alcohol, or illicit drugs. Blood pressure is 140/90 mm Hg and pulse is 56/min. BMI is 26 kg/m^2. Physical examination shows muscle weakness, predominantly of the shoulder and hip girdles. When the knee reflex is elicited, the quadriceps muscle contracts briskly but relaxation takes longer than normal. There are splitting and peeling of the nails. Serum creatine kinase is elevated. Which of the following tests is most likely to identify the cause of this patient's muscle weakness?

- A. 24-hour urinary cortisol excretion (12%)
- B. Acetylcholine receptor antibody titers (10%)
- C. CT scan of the chest (5%)
- D. Muscle biopsy (24%)
- ✓ E. Serum TSH level (46%)

Omitted
Correct answer
E

46%
Answered correctly

02 secs
Time Spent

03/31/2020
Last Updated

Explanation

Common causes of myopathy		
Disorder	Clinical features	Creatine kinase

Common causes of myopathy

Disorder	Clinical features	Creatine kinase
Glucocorticoid-induced myopathy	• Progressive proximal muscle weakness & atrophy **without pain** • Lower extremity muscles more involved	Normal
Polymyalgia rheumatica	• Muscle **pain & stiffness** in shoulder, neck & pelvic girdle • Worse in morning & with activity	Normal
Inflammatory myopathies (eg, polymyositis, dermatomyositis)	• Proximal muscle weakness • **Skin rash** & **inflammatory arthritis** possibly present	↑
Statin-induced myopathy	• Proximal muscle pain & weakness usually within weeks to months **after starting statin**	↑
Hypothyroid myopathy	• Muscle pain, cramps & weakness involving the proximal muscles • **Delayed tendon reflexes** & myoedema • Features of hypothyroidism	↑

An **elevated creatine kinase** (CK) level suggests a myopathic process with **myocyte damage** and release of muscle enzymes into the circulation. Common causes of myopathy with elevated CK include hypothyroidism, muscular dystrophies, inflammatory muscle diseases, and medications such as HMG-CoA reductase inhibitors.

This patient's fatigue, **weight gain**, **bradycardia**, and **brittle nails** are highly suggestive of **hypothyroid myopathy**. Decreased thyroid hormone

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31

An **elevated creatine kinase** (CK) level suggests a myopathic process with **myocyte damage** and release of muscle enzymes into the circulation. Common causes of myopathy with elevated CK include hypothyroidism, muscular dystrophies, inflammatory muscle diseases, and medications such as HMG-CoA reductase inhibitors.

This patient's fatigue, **weight gain**, **bradycardia**, and **brittle nails** are highly suggestive of **hypothyroid myopathy**. Decreased thyroid hormone levels impair muscle glycogen and triglyceride use and increase oxidative stress, resulting in myocyte injury. Patients typically presents with myalgias, proximal muscle weakness, decreased exercise tolerance, and cramping. **Myoedema** (focal muscle contraction at the site of percussion) and **delayed relaxation** of deep tendon reflexes are characteristic findings that are caused by impaired reuptake of calcium by the sarcoplasmic reticulum.

Hypothyroid myopathy and elevations in CK can be the first signs of hypothyroidism and can precede other manifestations by months to years. The diagnosis can be confirmed with an **elevated TSH level**.

(Choice A) A 24-hour urine cortisol test is used as an initial test for Cushing syndrome. This disorder can present with proximal muscle weakness and atrophy due to the direct catabolic effects of cortisol on skeletal muscle. However, there is no associated muscle pain or rise in CK, reflexes are normal, and other cushingoid features (eg, stria, dorsocervical fatty hypertrophy) are usually present.

(Choices B and C) Myasthenia gravis is caused by autoantibodies against nicotinic acetylcholine receptors on the postsynaptic membrane of the neuromuscular junction. It presents with fluctuating weakness that worsens through the day. Lambert-Eaton syndrome is a paraneoplastic disorder associated with small cell carcinoma of the lung (which can be identified on CT scan). It is caused by autoantibodies against voltage-gated calcium channels on the presynaptic membrane, which cause decreased release of acetylcholine. These disorders affect the neuromuscular junction rather than the muscle itself, and CK is normal.

(Choice D) Muscle biopsy is often needed for diagnosis of inflammatory myositis (eg, polymyositis, dermatomyositis). However, this patient has symptoms suggestive of hypothyroidism (eg, weight gain, bradycardia, brittle nails), and histologic findings in hypothyroid myopathy are often nonspecific.

Educational objective:
Hypothyroid myopathy presents with myalgias, proximal muscle weakness, elevated creatine kinase levels, and delayed relaxation of deep tendon reflexes. The diagnosis can be confirmed with an elevated TSH level. Other common causes of myopathy with elevated creatine kinase levels include inflammatory myopathies, muscular dystrophies, and HMG-CoA reductase inhibitors.

myalgias, proximal muscle weakness, decreased exercise tolerance, and cramping. **Myoedema** (focal muscle contraction at the site of percussion) and **delayed relaxation** of deep tendon reflexes are characteristic findings that are caused by impaired reuptake of calcium by the sarcoplasmic reticulum.

Hypothyroid myopathy and elevations in CK can be the first signs of hypothyroidism and can precede other manifestations by months to years. The diagnosis can be confirmed with an **elevated TSH level**.

(Choice A) A 24-hour urine cortisol test is used as an initial test for Cushing syndrome. This disorder can present with proximal muscle weakness and atrophy due to the direct catabolic effects of cortisol on skeletal muscle. However, there is no associated muscle pain or rise in CK, reflexes are normal, and other cushingoid features (eg, stria, dorsocervical fatty hypertrophy) are usually present.

(Choices B and C) Myasthenia gravis is caused by autoantibodies against nicotinic acetylcholine receptors on the postsynaptic membrane of the neuromuscular junction. It presents with fluctuating weakness that worsens through the day. Lambert-Eaton syndrome is a paraneoplastic disorder associated with small cell carcinoma of the lung (which can be identified on CT scan). It is caused by autoantibodies against voltage-gated calcium channels on the presynaptic membrane, which cause decreased release of acetylcholine. These disorders affect the neuromuscular junction rather than the muscle itself, and CK is normal.

(Choice D) Muscle biopsy is often needed for diagnosis of inflammatory myositis (eg, polymyositis, dermatomyositis). However, this patient has symptoms suggestive of hypothyroidism (eg, weight gain, bradycardia, brittle nails), and histologic findings in hypothyroid myopathy are often nonspecific.

Educational objective:
Hypothyroid myopathy presents with myalgias, proximal muscle weakness, elevated creatine kinase levels, and delayed relaxation of deep tendon reflexes. The diagnosis can be confirmed with an elevated TSH level. Other common causes of myopathy with elevated creatine kinase levels include inflammatory myopathies, muscular dystrophies, and HMG-CoA reductase inhibitors.

Pathophysiology	Endocrine, Diabetes & Metabolism	Hypothyroidism
Subject	System	Topic

Copyright © UWorld. All rights reserved.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31

A 6-year-old Caucasian girl is brought to your office by her mother. The mother says that her daughter is "womanly," including being exceptionally tall for her age. Physical examination reveals Tanner Stage 3 breast development and coarse pubic hair. The child's height is in the 96th percentile. You explain to her mother that, although this girl is very tall now, she will ultimately be shorter than average if she does not get treatment. Which of the following is the physiologic explanation for the information you provided?

A. Estrogen effect on the long bone diaphysis

B. Estrogen effect on the long bone epiphysis

C. Estrogen effect on the long bone epiphyseal plate

D. Somatomedin C effect on the long bone diaphysis

E. Somatomedin C effect on the long bone epiphyseal plate

Submit

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31

A 6-year-old Caucasian girl is brought to your office by her mother. The mother says that her daughter is "womanly," including being exceptionally tall for her age. Physical examination reveals Tanner Stage 3 breast development and coarse pubic hair. The child's height is in the 96th percentile. You explain to her mother that, although this girl is very tall now, she will ultimately be shorter than average if she does not get treatment. Which of the following is the physiologic explanation for the information you provided?

A. Estrogen effect on the long bone diaphysis (2%)

B. Estrogen effect on the long bone epiphysis (6%)

✓ C. Estrogen effect on the long bone epiphyseal plate (77%)

D. Somatomedin C effect on the long bone diaphysis (1%)

E. Somatomedin C effect on the long bone epiphyseal plate (11%)

Omitted
Correct answer
C

77%
Answered correctly

02 secs
Time Spent

01/13/2020
Last Updated

Explanation

The child described in the vignette is six years old and has already undergone pubertal changes, as indicated by her Tanner staging. (Also called the sexual maturity rating, Tanner staging is a systematic, universalized method that uses female breast and pubic hair development to categorize development.) Precocious puberty in Caucasian females is defined as the development of secondary sexual characters at an age less than seven years.

Young bone has several layers; their order from middle to end is diaphysis, metaphysis, epiphyseal cartilage, and epiphysis. The epiphyseal cartilage, also called the "growth plate, is responsible for linear growth.

The child described in the vignette is six years old and has already undergone pubertal changes, as indicated by her Tanner staging. (Also called the sexual maturity rating, Tanner staging is a systematic, universalized method that uses female breast and pubic hair development to categorize development.) Precocious puberty in Caucasian females is defined as the development of secondary sexual characters at an age less than seven years.

Young bone has several layers; their order from middle to end is diaphysis, metaphysis, epiphyseal cartilage, and epiphysis. The epiphyseal cartilage, also called the "growth plate, is responsible for linear growth.

Linear growth stops when the epiphyseal growth plate closes, i.e. when the epiphysis fuses with the metaphysis. Sex steroids initially increase linear growth, but they also encourage closure of epiphyseal growth plates. Once the growth plates have closed, linear growth is irreversibly stopped. In normal puberty, there is a rapid increase in growth. At the end of this pubertal growth spurt, almost 90% of the final height is achieved. Although this child is currently taller than her peers, the excess steroids will soon cause epiphyseal growth plate closure; hence, if this patient is not treated, she will ultimately not meet her full growth potential.

(Choices A and B) In sites other than the epiphyseal growth plate, the effect of estrogen on bone is anabolic because estrogen increases osteoblastic bone deposition and decreases osteoclastic bone resorption. Low estrogenic states, such as menopause, are associated with rapid bone loss.

(Choices D and E) The secretion of somatomedin C, more commonly known as insulin-like growth factor-1 (IGF-1), is directly increased when growth hormone is secreted from the pituitary gland. IGF-1 causes the differentiation and proliferation of chondrocytes in the epiphyseal growth plate, causing an increase in linear growth. However, unlike estrogen, IGF-1 does not accelerate epiphyseal closure.

Educational Objective:
Sex hormones promote both growth and epiphyseal plate closure; hence, precocious puberty may result in a shorter stature, despite an initial growth spurt. Gigantism is caused by excessive pituitary production of growth hormone; these patients achieve enormous heights because, unlike excessive sex steroids, excessive IGF-1 does not lead to premature closure of the epiphysis.

Pathophysiology	Endocrine, Diabetes & Metabolism	Precocious puberty
Subject	System	Topic

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31

A 2-year-old girl is brought to the clinic by her mother for evaluation of ambiguous genitalia. She was born with clitoral enlargement and partial fusion of the labioscrotal folds. The patient has also had high blood pressure recorded on 3 consecutive office visits. She has been tracking at the 50th percentile for height and weight, and has not had any other medical problems. Family history is noncontributory. Laboratory studies are significant for moderate hypokalemia. Cytogenetic studies show a 46,XX karyotype. Which of the following enzymes is most likely deficient in this patient?

A. 5α-reductase

B. 11β-hydroxylase

C. 17α-hydroxylase

D. 21-hydroxylase

E. Side-chain cleavage enzyme

Submit

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31

A 2-year-old girl is brought to the clinic by her mother for evaluation of ambiguous genitalia. She was born with clitoral enlargement and partial fusion of the labioscrotal folds. The patient has also had high blood pressure recorded on 3 consecutive office visits. She has been tracking at the 50th percentile for height and weight, and has not had any other medical problems. Family history is noncontributory. Laboratory studies are significant for moderate hypokalemia. Cytogenetic studies show a 46,XX karyotype. Which of the following enzymes is most likely deficient in this patient?

A. 5α-reductase (1%)
✓ B. 11β-hydroxylase (56%)
C. 17α-hydroxylase (21%)
D. 21-hydroxylase (20%)
E. Side-chain cleavage enzyme (0%)

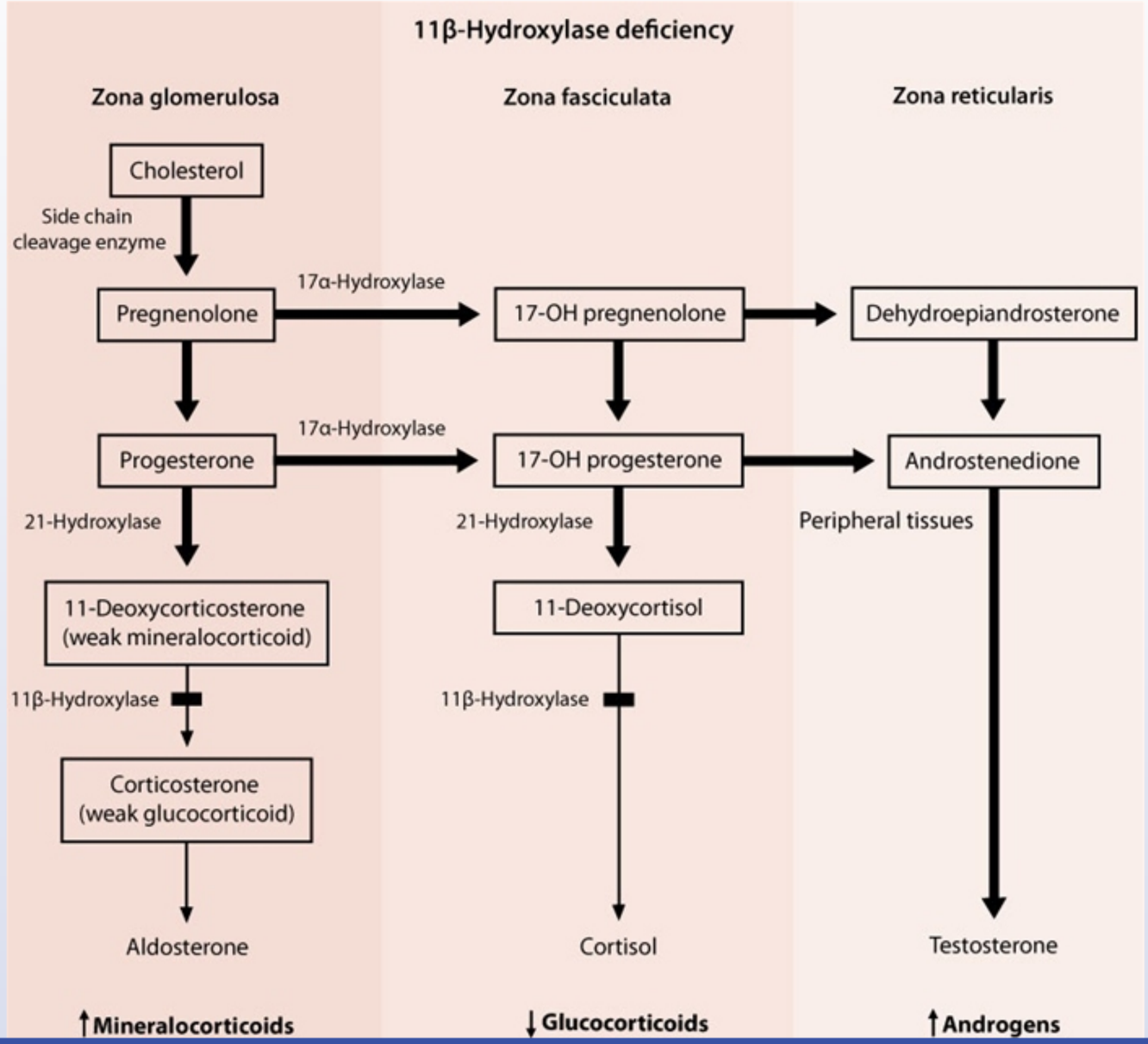
Omitted
Correct answer
B

56%
Answered correctly

01 sec
Time Spent

01/23/2020
Last Updated

Explanation


11β-Hydroxylase deficiency
Zona glomerulosa
Zona fasciculata
Zona reticularis
Cholesterol
Side chain cleavage enzyme
Pregnenolone
17α-Hydroxylase
17-OH pregnenolone
Dehydroepiandrosterone
Progesterone
17α-Hydroxylase
17-OH progesterone
Androstenedione
21-Hydroxylase
21-Hydroxylase
Peripheral tissues
11-Deoxycorticosterone (weak mineralocorticoid)
11-Deoxycortisol
11β-Hydroxylase
11β-Hydroxylase
Corticosterone (weak glucocorticoid)
Aldosterone
Cortisol
Testosterone
↑Mineralocorticoids
↓Glucocorticoids
↑Androgens

This girl with ambiguous genitalia, hypertension, and hypokalemia most likely has **11β-hydroxylase deficiency**, the second-most common cause of congenital adrenal hyperplasia after 21-hydroxylase deficiency.

11β-hydroxylase is responsible for converting 11-deoxycorticosterone to corticosterone and 11-deoxycortisol to cortisol. Enzyme deficiency results in the buildup of aldosterone and cortisol precursors, which are then shunted toward adrenal androgen synthesis. In genetically female infants, **androgen excess** leads to **ambiguous genitalia** (virilization). Although 11β-hydroxylase deficiency inhibits aldosterone synthesis, **11-deoxycorticosterone** accumulates and acts as a weak mineralocorticoid, causing affected individuals to have **hypertension** and **hypokalemia**.

(Choice A) 5α-reductase deficiency causes ambiguous genitalia in boys due to the defective conversion of testosterone to dihydrotestosterone. Girls have normal genitalia, and blood pressure and electrolytes are unaffected.

(Choice C) 17α-hydroxylase deficiency results in impaired sex steroid and cortisol synthesis, and increased production of mineralocorticoids. Girls are born with normal genitalia, but boys are born undervirilized (ambiguous genitalia). Affected individuals develop hypertension and hypokalemia (mineralocorticoid excess) and do not undergo puberty (no sex steroids).

(Choice D) 21-hydroxylase deficiency decreases glucocorticoid and mineralocorticoid synthesis and increases adrenal androgen production. Girls are born with ambiguous genitalia (androgen excess) and frequently develop hypotension and hyperkalemia (mineralocorticoid deficiency).

(Choice E) Side-chain cleavage enzyme converts cholesterol to pregnenolone. Because this is the first enzyme in the steroidogenic pathway, deficiency impairs synthesis of all steroid hormones. Complete deficiency is lethal due to absent placental progesterone synthesis.

Educational objective:
11β-hydroxylase deficiency typically results in excessive adrenal androgen and mineralocorticoid (11-deoxycorticosterone) production. Genetically female infants are born with ambiguous genitalia, and affected individuals develop hypertension and hypokalemia early in life.

References

- Clinical perspectives in congenital adrenal hyperplasia due to 11ß-hydroxylase deficiency.

Pathophysiology	Endocrine, Diabetes & Metabolism	Congenital adrenal hyperplasia
Subject	System	Topic

Copyright © UWorld. All rights reserved.

This girl with ambiguous genitalia, hypertension, and hypokalemia most likely has **11ß-hydroxylase deficiency**, the second-most common cause

Exhibit Display

Enzyme deficiency	Hormonal abnormalities	Symptoms
21-hydroxylase	• ↓Cortisol & aldosterone • ↑Testosterone • ↑17-hydroxyprogesterone	• Ambiguous genitalia in girls • Salt wasting (vomiting, hypotension, ↓Na^+, ↑K^+)
11β-hydroxylase	• ↓Cortisol & aldosterone • ↑Testosterone • ↑11-deoxycorticosterone (weak mineralocorticoid) & 11- deoxycortisol	• Ambiguous genitalia in girls • Fluid & salt retention, hypertension
17α-hydroxylase	• ↓Cortisol & testosterone • ↑Mineralocorticoids • ↑Corticosterone (weak glucocorticoid)	• All patients phenotypically female • Fluid & salt retention, hypertension

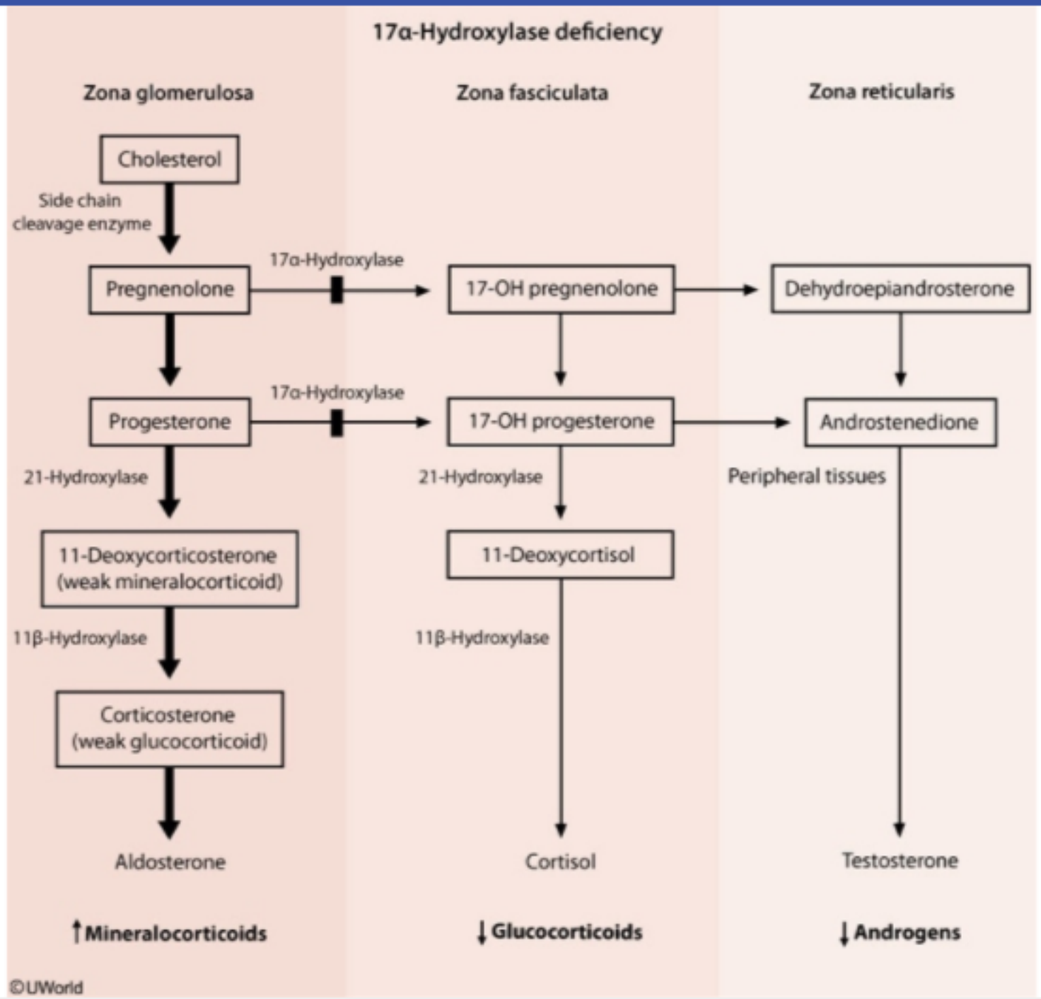
©UWorld

Zoom In | Zoom Out | Reset | Add To New Card | Existing Card

Copyright © UWorld. All rights reserved.

This girl with ambiguous genitalia, hypertension, and hypokalemia most likely has **11ß-hydroxylase deficiency**, the second-most common cause

Exhibit Display

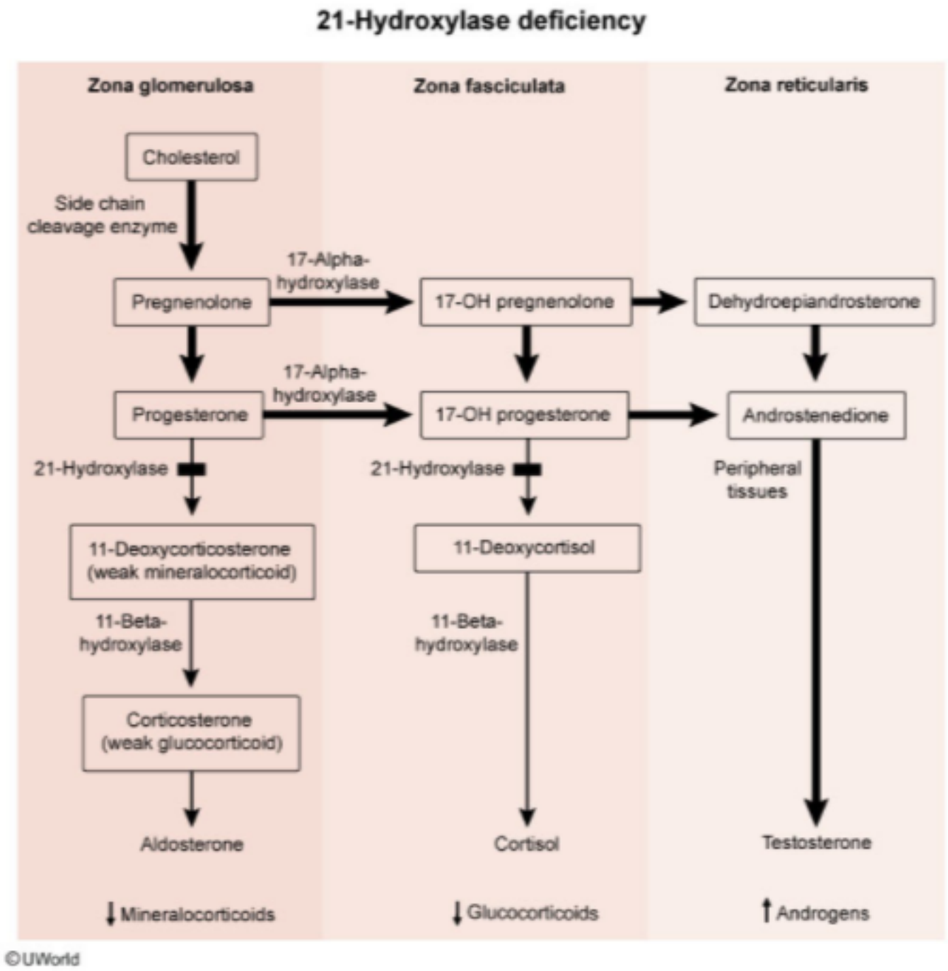


Zoom In | Zoom Out | Reset | Add To New Card | Existing Card

Copyright © UWorld. All rights reserved.

This girl with ambiguous genitalia, hypertension, and hypokalemia most likely has **11ß-hydroxylase deficiency**, the second-most common cause

Exhibit Display

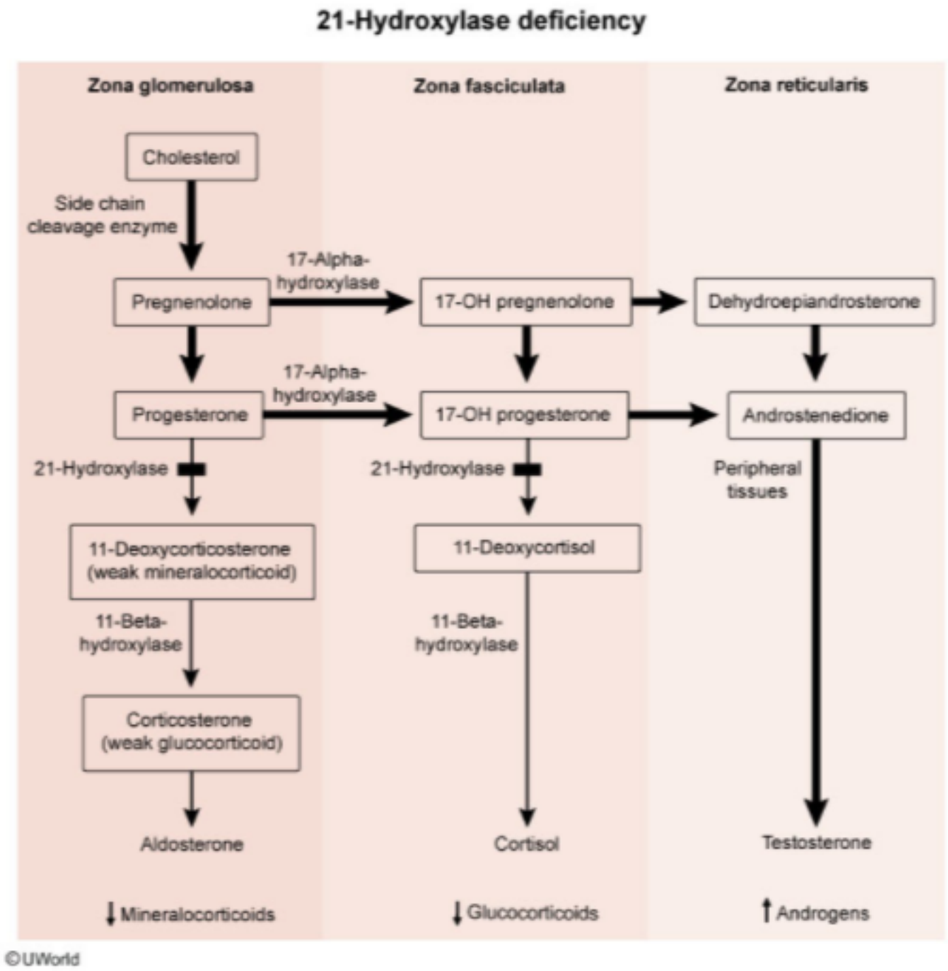


Zoom In | Zoom Out | Reset | Add To New Card | Existing Card

Copyright © UWorld. All rights reserved.

This girl with ambiguous genitalia, hypertension, and hypokalemia most likely has **11ß-hydroxylase deficiency**, the second-most common cause

Exhibit Display

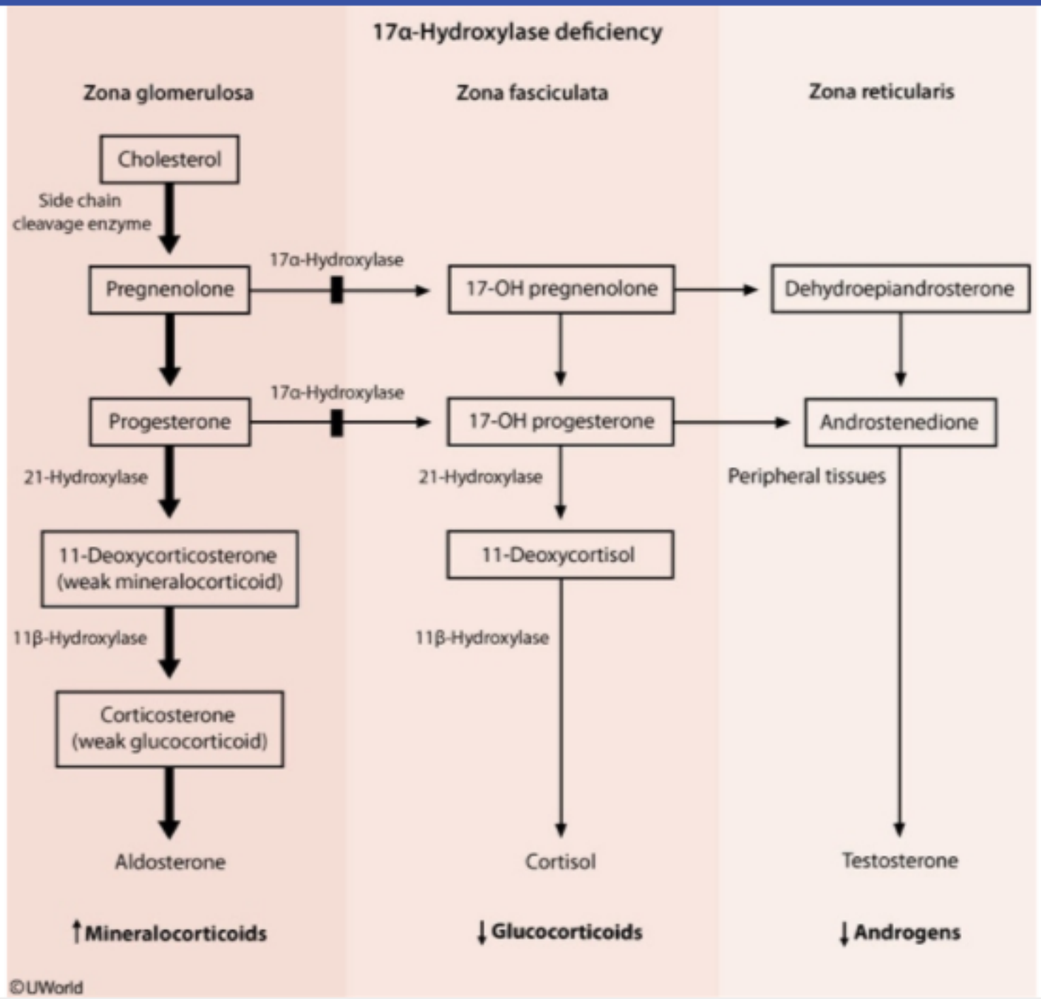


Zoom In | Zoom Out | Reset | Add To New Card | Existing Card

Copyright © UWorld. All rights reserved.

This girl with ambiguous genitalia, hypertension, and hypokalemia most likely has **11ß-hydroxylase deficiency**, the second-most common cause

Exhibit Display



Zoom In | Zoom Out | Reset | Add To New Card | Existing Card

Copyright © UWorld. All rights reserved.

A 30-year-old woman has had diarrhea and weight loss for the past several months. She also has diffuse bone pain and generalized weakness. The patient has a history of primary hypothyroidism for which she takes levothyroxine. She is 162.5 cm (5 ft 4 in) tall and weighs 45 kg (99.2 lb). BMI is 17 kg/m^2. On physical examination, the abdomen is soft and nontender. Initial laboratory evaluation reveals microcytic anemia, hypoalbuminemia, normal magnesium level, and normal serum TSH concentration. The patient is found to have positive anti-tissue transglutaminase IgA antibodies. Which of the following sets of additional laboratory findings are most likely present in this patient?

	Serum calcium	Serum phosphorus	Serum parathyroid hormone
A.	↑	↓	↑
B.	↓	↓	↑
C.	↓	↑	↓
D.	↓	↑	↑
E.	normal	↑	↑

Submit

A 30-year-old woman has had diarrhea and weight loss for the past several months. She also has diffuse bone pain and generalized weakness. The patient has a history of primary hypothyroidism for which she takes levothyroxine. She is 162.5 cm (5 ft 4 in) tall and weighs 45 kg (99.2 lb). BMI is 17 kg/m^2. On physical examination, the abdomen is soft and nontender. Initial laboratory evaluation reveals microcytic anemia, hypoalbuminemia, normal magnesium level, and normal serum TSH concentration. The patient is found to have positive anti-tissue transglutaminase IgA antibodies. Which of the following sets of additional laboratory findings are most likely present in this patient?

	Serum calcium	Serum phosphorus	Serum parathyroid hormone
A. (25%)	↑	↓	↑
✓ B. (41%)	↓	↓	↑
C. (11%)	↓	↑	↓
D. (18%)	↓	↑	↑
E. (3%)	normal	↑	↑

Omitted
Correct answer
B

41%
Answered correctly

03 secs
Time Spent

03/06/2020
Last Updated

Explanation

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31

Explanation

This patient with diarrhea, weight loss, and a positive tissue transglutaminase antibody assay has celiac disease, an immune-mediated hypersensitivity to dietary gluten. **Celiac disease** is characterized by villous atrophy in the small intestine, leading to **malabsorption** of dietary fats and fat-soluble vitamins (ie, A, D, E, K). The resulting **vitamin D deficiency** can present as rickets in children and osteomalacia in adults.

Vitamin D increases intestinal absorption of calcium and phosphorus; deficiency reduces calcium absorption, which in turn stimulates release of parathyroid hormone (PTH). Vitamin D also directly inhibits PTH release, and therefore vitamin D deficiency facilitates a significant rise in PTH (secondary hyperparathyroidism). PTH induces release of calcium and phosphorus from bones, leading to decreased bone mineralization. (Although most phosphorus in the body is in the form of hydroxyapatite in bone, circulating phosphorus is primarily in the form of phosphate/phosphoric acids.)

Typical laboratory findings in vitamin D deficiency include:

- **low 25-hydroxyvitamin D**, which reflects total body vitamin D stores (PTH stimulates renal conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D; therefore, 1,25-dihydroxyvitamin D may remain within laboratory norms).
- **elevated PTH**.
- increased alkaline phosphatase, reflecting increased bone turnover.
- **low serum phosphorus**, due to decreased intestinal absorption and increased PTH-mediated renal excretion.

PTH may initially maintain normal serum calcium levels by reducing urinary calcium excretion. However, hypocalcemia may eventually develop as bone stores are depleted in later or more severe cases.

(Choice A) Primary hyperparathyroidism presents with elevated PTH, mild hypercalcemia, and low serum phosphorus (due to increased renal excretion) but is usually due to a parathyroid adenoma and is not associated with celiac disease.

(Choice C) In hypoparathyroidism, low serum PTH is accompanied by hypocalcemia and an increase in serum phosphorus. Hypoparathyroidism can be caused by severe hypomagnesemia, which can be seen with prolonged diarrhea, but this patient's magnesium level is normal.

(Choices D and E) Chronic kidney disease causes hyperphosphatemia due to decreased filtration and excretion of phosphate. Concurrently, there is decreased renal production of 1,25-dihydroxyvitamin D (the activated form) due to inadequate renal metabolic activity and suppression of

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31

dihydroxyvitamin D, therefore, 1,25-dihydroxyvitamin D may remain within laboratory norms).

- **elevated PTH**.
- increased alkaline phosphatase, reflecting increased bone turnover.
- **low serum phosphorus**, due to decreased intestinal absorption and increased PTH-mediated renal excretion.

PTH may initially maintain normal serum calcium levels by reducing urinary calcium excretion. However, hypocalcemia may eventually develop as bone stores are depleted in later or more severe cases.

(Choice A) Primary hyperparathyroidism presents with elevated PTH, mild hypercalcemia, and low serum phosphorus (due to increased renal excretion) but is usually due to a parathyroid adenoma and is not associated with celiac disease.

(Choice C) In hypoparathyroidism, low serum PTH is accompanied by hypocalcemia and an increase in serum phosphorus. Hypoparathyroidism can be caused by severe hypomagnesemia, which can be seen with prolonged diarrhea, but this patient's magnesium level is normal.

(Choices D and E) Chronic kidney disease causes hyperphosphatemia due to decreased filtration and excretion of phosphate. Concurrently, there is decreased renal production of 1,25-dihydroxyvitamin D (the activated form) due to inadequate renal metabolic activity and suppression of 1-alpha-hydroxylase by hyperphosphatemia. Hypocalcemia may be present, although increased PTH sometimes maintains calcium within laboratory norms. Pseudohypoparathyroidism is characterized by resistance to PTH and presents with similar biochemical markers.

Educational objective:
Malabsorption caused by celiac disease can lead to vitamin D deficiency. Patients have decreased serum phosphorus, increased serum parathyroid hormone (secondary hyperparathyroidism), and low (or normal) serum calcium.

References

- Osteomalacia as a result of vitamin D deficiency

Pathophysiology	Endocrine, Diabetes & Metabolism	Vitamin D deficiency
Subject	System	Topic

Copyright © UWorld. All rights reserved.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31

A 13-year-old boy is evaluated for abnormal growth. His mother says that he has grown rapidly over the past 10 months and is much taller than his older brother and other children his age. During this time, she has had a hard time finding clothes that fit him and has had to buy new shoes for him each month due to increasing foot size. The patient says that he feels well except for excessive sweating. He has no history of major medical illness and takes no medications. Both parents are of average height and have normally proportioned limbs. The patient is above the 99th percentile for height and at the 90th percentile for weight. On physical examination, he has long extremities with large hands and feet; the lower jaw is protruding. Heart sounds are normal. Sexual development is Tanner stage 4. Which of the following is the most likely underlying cause of this patient's condition?

A. Aneuploidy of the X chromosome
B. De novo mutation in the fibrillin-1 gene
C. Defective growth hormone receptor
D. Excessive liver production of IGF-1
E. Excessive thyroxine production
F. Increased hypothalamic release of IGF-1
G. Increased pituitary gonadotropin release

Submit

A 13-year-old boy is evaluated for abnormal growth. His mother says that he has grown rapidly over the past 10 months and is much taller than his older brother and other children his age. During this time, she has had a hard time finding clothes that fit him and has had to buy new shoes for him each month due to increasing foot size. The patient says that he feels well except for excessive sweating. He has no history of major medical illness and takes no medications. Both parents are of average height and have normally proportioned limbs. The patient is above the 99th percentile for height and at the 90th percentile for weight. On physical examination, he has long extremities with large hands and feet; the lower jaw is protruding. Heart sounds are normal. Sexual development is Tanner stage 4. Which of the following is the most likely underlying cause of this patient's condition?

- A. Aneuploidy of the X chromosome (3%)
- B. De novo mutation in the fibrillin-1 gene (5%)
- C. Defective growth hormone receptor (5%)
- ✓ D. Excessive liver production of IGF-1 (58%)
- E. Excessive thyroxine production (1%)
- F. Increased hypothalamic release of IGF-1 (13%)
- G. Increased pituitary gonadotropin release (11%)

Omitted
Correct answer
D

58%
Answered correctly

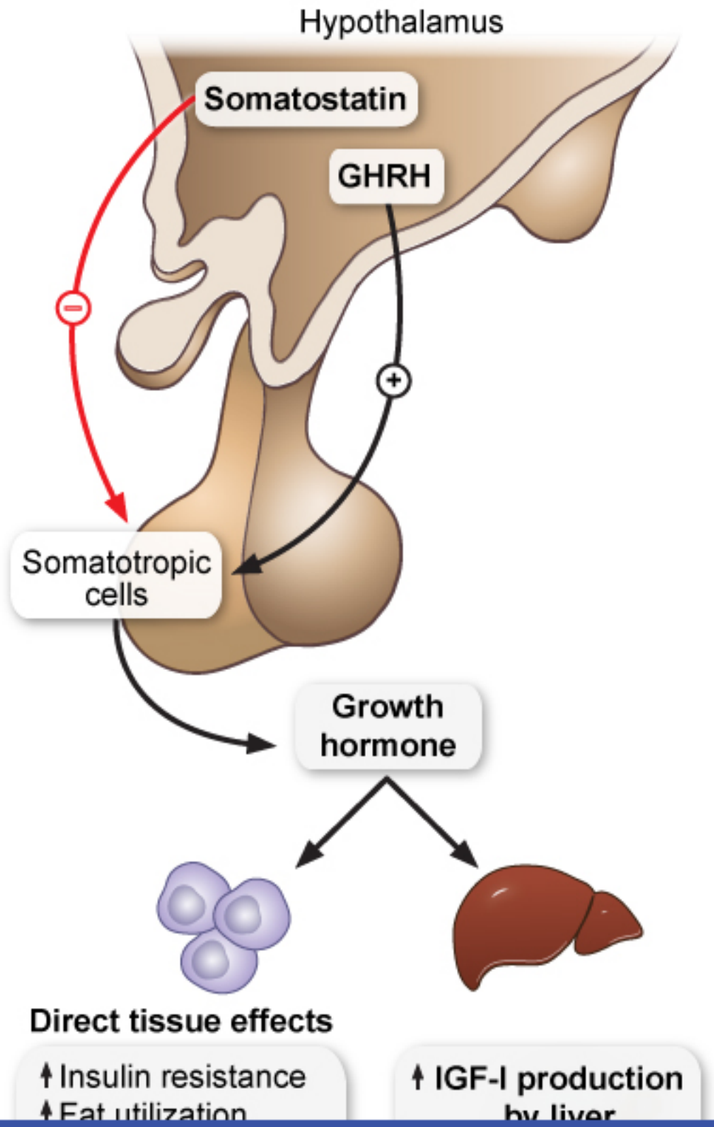
02 secs
Time Spent

05/04/2020
Last Updated

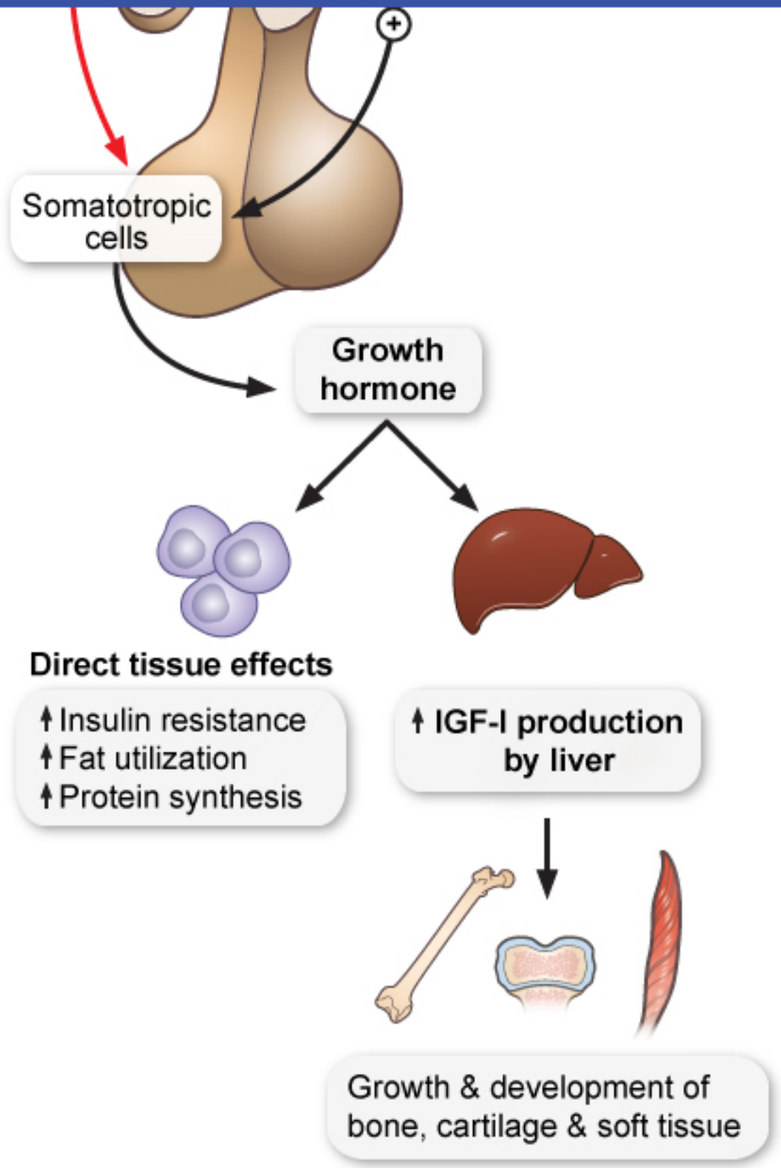
Explanation

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31

Growth hormone effects



1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31



GHRH = growth hormone-releasing hormone.

©UWorld

This patient most likely has **gigantism**, a condition caused by hypersecretion of **growth hormone (GH)** during childhood. GH is a peptide hormone secreted by the anterior pituitary that acts as both a growth promoter and stress hormone (increasing glucose and free fatty acid levels). Although GH has direct effects on target tissue (eg, chondrogenesis, myocyte protein synthesis), its growth-promoting effects are primarily mediated by **insulin-like growth factor-1 (IGF-1)**, which is released from the liver following stimulation of hepatic GH receptors. IGF-1 binds to a specific receptor tyrosine kinase and stimulates cell growth and proliferation in bone, cartilage, skeletal muscle, and other soft tissues.

Gigantism occurs in children and adolescents before fusion of the epiphyseal growth plates, resulting in **rapid linear growth** along with large hands and feet, thickening of the calvarium, protrusion of the jaw (**prognathism**), excessive sweating, and oily skin. The adult variant, acromegaly, has no effect on stature because the epiphyseal growth plates have already fused.

(Choices A and B) Klinefelter syndrome is caused by a nondisjunction of sex chromosomes (47,XXY). Patients are phenotypically male with hypogonadism and infertility. Marfan syndrome is caused by a defect in fibrillin-1 and presents with joint hypermobility, increased limb length, and arachnodactyly. These disorders are associated with tall stature but do not exhibit prognathism or bony enlargement of the hands and feet.

(Choice C) Defects in the GH receptor cause Laron dwarfism, characterized by decreased linear growth, high serum GH concentrations, and low levels of circulating IGF-1.

(Choice E) Excessive thyroxine production (ie, hyperthyroidism) presents with weight loss, heat intolerance, and tremor. Sweating is common, but hyperthyroidism in children causes short stature, not accelerated growth.

(Choice F) Circulating levels of IGF-1 are produced primarily in the liver. Although IGF-1 is also produced locally in the hypothalamus to regulate central nervous system activity, this source does not contribute significantly to bone and soft-tissue growth.

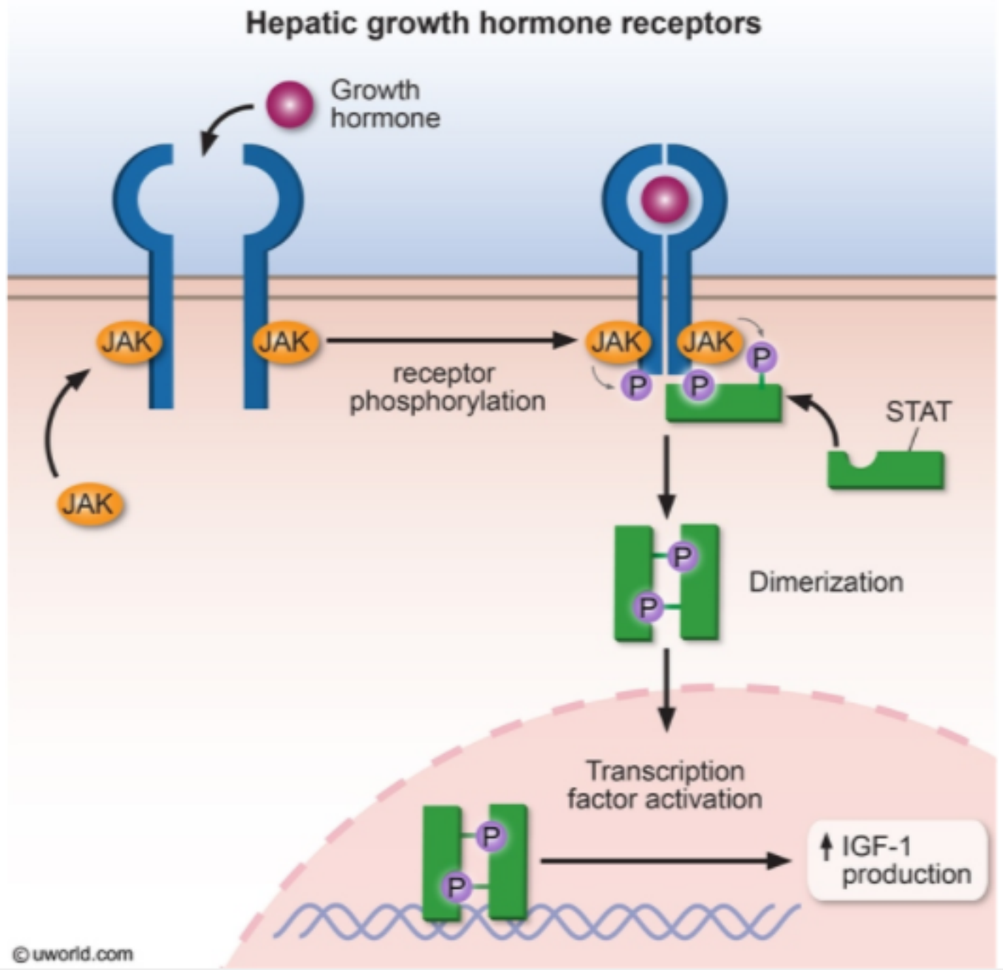
(Choice G) Increased pituitary gonadotropin release causes central precocious puberty. This patient has appropriate sexual development for age.

Educational objective:
Gigantism is caused by excess growth hormone (GH) during childhood and is characterized by accelerated linear growth, prognathism, and bony enlargement of the hands and feet. GH excess after closure of the epiphysial growth plates causes acromegaly. GH has direct effects on target tissues and indirect effects mediated by insulin-like growth factor-1 secretion from the liver.

References

©UWorld

Exhibit Display

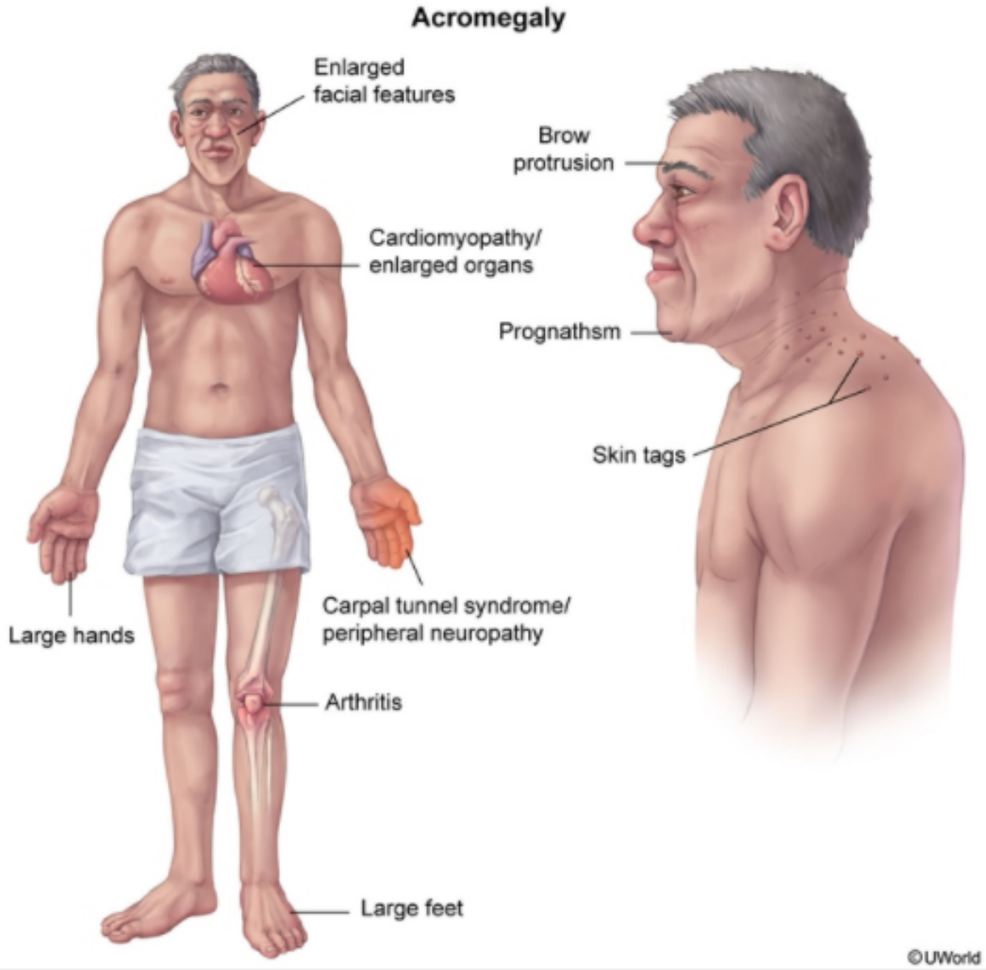


Zoom In | Zoom Out | Reset | Add To New Card | Existing Card

References

©UWorld

Exhibit Display



Zoom In | Zoom Out | Reset | Add To New Card | Existing Card

hands and feet, thickening of the calvarium, protrusion of the jaw (**prognathism**), excessive sweating, and oily skin. The adult variant, acromegaly, has no effect on stature because the epiphyseal growth plates have already fused.

(Choices A and B) Klinefelter syndrome is caused by a nondisjunction of sex chromosomes (47,XXY). Patients are phenotypically male with hypogonadism and infertility. Marfan syndrome is caused by a defect in fibrillin-1 and presents with joint hypermobility, increased limb length, and arachnodactyly. These disorders are associated with tall stature but do not exhibit prognathism or bony enlargement of the hands and feet.

(Choice C) Defects in the GH receptor cause Laron dwarfism, characterized by decreased linear growth, high serum GH concentrations, and low levels of circulating IGF-1.

(Choice E) Excessive thyroxine production (ie, hyperthyroidism) presents with weight loss, heat intolerance, and tremor. Sweating is common, but hyperthyroidism in children causes short stature, not accelerated growth.

(Choice F) Circulating levels of IGF-1 are produced primarily in the liver. Although IGF-1 is also produced locally in the hypothalamus to regulate central nervous system activity, this source does not contribute significantly to bone and soft-tissue growth.

(Choice G) Increased pituitary gonadotropin release causes central precocious puberty. This patient has appropriate sexual development for age.

Educational objective:
Gigantism is caused by excess growth hormone (GH) during childhood and is characterized by accelerated linear growth, prognathism, and bony enlargement of the hands and feet. GH excess after closure of the epiphysial growth plates causes acromegaly. GH has direct effects on target tissues and indirect effects mediated by insulin-like growth factor-1 secretion from the liver.

References

- Pituitary gigantism: causes and clinical characteristics.

Pathophysiology	Endocrine, Diabetes & Metabolism	Acromegaly
Subject	System	Topic

Copyright © UWorld. All rights reserved.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31

A 29-year-old woman comes to the office due to increased hair loss. She delivered a healthy baby boy 8 months ago and has not felt the same since. The patient has fatigue and decreased libido, and her menstrual cycles have not returned. She has no prior medical problems and no drug allergies. The patient takes a multivitamin and does not use tobacco, alcohol, or illicit drugs. There is no significant family history. Blood pressure is 110/70 mm Hg and pulse is 58/min. Physical examination shows diffuse alopecia and thickened, brittle nails. The thyroid is nontender. Laboratory results show decreased serum TSH and free thyroxine (T4) levels. Which of the following is the most likely diagnosis in this patient?

A. Chronic autoimmune (Hashimoto) thyroiditis
B. Graves disease
C. Postpartum thyroiditis
D. Secondary hyperthyroidism
E. Secondary hypothyroidism
F. Subacute granulomatous (de Quervain) thyroiditis

Submit

A 29-year-old woman comes to the office due to increased hair loss. She delivered a healthy baby boy 8 months ago and has not felt the same since. The patient has fatigue and decreased libido, and her menstrual cycles have not returned. She has no prior medical problems and no drug allergies. The patient takes a multivitamin and does not use tobacco, alcohol, or illicit drugs. There is no significant family history. Blood pressure is 110/70 mm Hg and pulse is 58/min. Physical examination shows diffuse alopecia and thickened, brittle nails. The thyroid is nontender. Laboratory results show decreased serum TSH and free thyroxine (T4) levels. Which of the following is the most likely diagnosis in this patient?

A. Chronic autoimmune (Hashimoto) thyroiditis (4%)
B. Graves disease (1%)
C. Postpartum thyroiditis (31%)
D. Secondary hyperthyroidism (2%)
✓ E. Secondary hypothyroidism (59%)
F. Subacute granulomatous (de Quervain) thyroiditis (1%)

Omitted
Correct answer
E

59%
Answered correctly

02 secs
Time Spent

02/12/2020
Last Updated

Explanation

Central hypothyroidism	
	• Mass lesions (eg, pituitary adenoma) • Pituitary surgery, trauma, irradiation

Central hypothyroidism	
Causes	• Mass lesions (eg, pituitary adenoma) • Pituitary surgery, trauma, irradiation • Infiltrative disorders (eg, sarcoidosis, hemochromatosis) • Pituitary infarction (eg, Sheehan syndrome)
Clinical features	• Hypothyroid symptoms • Mass-effect symptoms (eg, headache, visual field defects) if due to mass
Hormone levels	• Low free thyroxine (T4) • Low or inappropriately normal TSH • Other pituitary hormone deficiencies (eg, ACTH, prolactin, gonadotropins)

This patient has hypothyroidism manifesting as fatigue, hair loss, and brittle nails with a low serum thyroxine (T4) level. The **low TSH** confirms that this is due to hypothalamic-pituitary dysfunction (ie, **central/secondary hypothyroidism**) rather than a primary thyroid disorder, which would cause a compensatory rise in TSH. Central hypothyroidism is much less common than primary hypothyroidism. However, when it occurs, other hypothalamic-pituitary systems may be affected and patients may develop deficiencies of other pituitary hormones (eg, low gonadotropin levels leading to amenorrhea).

The causes of central hypothyroidism are the same as those of hypopituitarism in general. **Sheehan syndrome** is ischemic necrosis of the pituitary gland and is typically caused by systemic hypotension during delivery. During pregnancy, the pituitary gland enlarges due to estrogen-induced hyperplasia of lactotrophs, but the blood supply does not increase proportionally. Subsequent **peripartum hemorrhage with hypotension** can cause underperfusion of the pituitary gland with subsequent ischemic injury.

(Choices A and C) Chronic autoimmune (Hashimoto) thyroiditis is the most common cause of hypothyroidism. Postpartum thyroiditis is a variant of Hashimoto thyroiditis that occurs within a year of pregnancy. These disorders cause primary hypothyroidism with elevated TSH levels.

(Choice B) Graves disease is an autoimmune disorder caused by activating antibodies against the TSH receptor. It presents with elevated T4

This patient has hypothyroidism manifesting as fatigue, hair loss, and brittle nails with a low serum thyroxine (T4) level. The **low TSH** confirms that this is due to hypothalamic-pituitary dysfunction (ie, **central/secondary hypothyroidism**) rather than a primary thyroid disorder, which would cause a compensatory rise in TSH. Central hypothyroidism is much less common than primary hypothyroidism. However, when it occurs, other hypothalamic-pituitary systems may be affected and patients may develop deficiencies of other pituitary hormones (eg, low gonadotropin levels leading to amenorrhea).

The causes of central hypothyroidism are the same as those of hypopituitarism in general. **Sheehan syndrome** is ischemic necrosis of the pituitary gland and is typically caused by systemic hypotension during delivery. During pregnancy, the pituitary gland enlarges due to estrogen-induced hyperplasia of lactotrophs, but the blood supply does not increase proportionally. Subsequent **peripartum hemorrhage with hypotension** can cause underperfusion of the pituitary gland with subsequent ischemic injury.

(Choices A and C) Chronic autoimmune (Hashimoto) thyroiditis is the most common cause of hypothyroidism. Postpartum thyroiditis is a variant of Hashimoto thyroiditis that occurs within a year of pregnancy. These disorders cause primary hypothyroidism with elevated TSH levels.

(Choice B) Graves disease is an autoimmune disorder caused by activating antibodies against the TSH receptor. It presents with elevated T4 and suppressed TSH levels, typically with a goiter and ocular manifestations (eg, proptosis, lid lag).

(Choice D) Secondary (central) hyperthyroidism is a rare disorder, usually caused by a TSH-secreting pituitary adenoma. Both TSH and serum T4 levels are elevated.

(Choice F) Subacute granulomatous (de Quervain) thyroiditis causes a painful goiter and transient hyperthyroid symptoms; it typically follows a viral syndrome.

Educational objective:
Central hypothyroidism is characterized by low serum TSH and thyroxine (T4) levels and is due to hypothalamic-pituitary dysfunction. Sheehan syndrome is ischemic necrosis of the pituitary gland and is typically caused by systemic hypotension during delivery. In addition to central hypothyroidism, patients may also develop deficiencies of other pituitary hormones (eg, ACTH, prolactin, gonadotropins).

References

- Clinical review: central hypothyroidism: pathogenic, diagnostic, and therapeutic challenges.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31

leading to amenorrhea).

The causes of central hypothyroidism are the same as those of hypopituitarism in general. **Sheehan syndrome** is ischemic necrosis of the pituitary gland and is typically caused by systemic hypotension during delivery. During pregnancy, the pituitary gland enlarges due to estrogen-induced hyperplasia of lactotrophs, but the blood supply does not increase proportionally. Subsequent **peripartum hemorrhage with hypotension** can cause underperfusion of the pituitary gland with subsequent ischemic injury.

(Choices A and C) Chronic autoimmune (Hashimoto) thyroiditis is the most common cause of hypothyroidism. Postpartum thyroiditis is a variant of Hashimoto thyroiditis that occurs within a year of pregnancy. These disorders cause primary hypothyroidism with elevated TSH levels.

(Choice B) Graves disease is an autoimmune disorder caused by activating antibodies against the TSH receptor. It presents with elevated T4 and suppressed TSH levels, typically with a goiter and ocular manifestations (eg, proptosis, lid lag).

(Choice D) Secondary (central) hyperthyroidism is a rare disorder, usually caused by a TSH-secreting pituitary adenoma. Both TSH and serum T4 levels are elevated.

(Choice F) Subacute granulomatous (de Quervain) thyroiditis causes a painful goiter and transient hyperthyroid symptoms; it typically follows a viral syndrome.

Educational objective:
Central hypothyroidism is characterized by low serum TSH and thyroxine (T4) levels and is due to hypothalamic-pituitary dysfunction. Sheehan syndrome is ischemic necrosis of the pituitary gland and is typically caused by systemic hypotension during delivery. In addition to central hypothyroidism, patients may also develop deficiencies of other pituitary hormones (eg, ACTH, prolactin, gonadotropins).

References

- Clinical review: central hypothyroidism: pathogenic, diagnostic, and therapeutic challenges.

Pathophysiology	Endocrine, Diabetes & Metabolism	Hypothyroidism
Subject	System	Topic

Copyright © UWorld. All rights reserved.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31

A 40-year-old woman is hospitalized due to a femoral neck fracture that occurred when she slipped while stepping out of the bathtub. The patient was diagnosed with a prolactinoma 3 years ago during evaluation of amenorrhea, but she refused medical or surgical treatments. The tumor is being monitored closely and has not increased in size or caused any visual symptoms. The patient has no other medical problems, takes no medications, and does not use tobacco, alcohol, or illicit drugs. She has 3 healthy children and no significant family history. The underlying mechanism for this patient's susceptibility to fracture is most likely to cause which of the following additional manifestations?

A. Hand tremors

B. Kidney stones

C. Stomach ulcers

D. Swallowing difficulty

E. Vaginal dryness

Submit

A 40-year-old woman is hospitalized due to a femoral neck fracture that occurred when she slipped while stepping out of the bathtub. The patient was diagnosed with a prolactinoma 3 years ago during evaluation of amenorrhea, but she refused medical or surgical treatments. The tumor is being monitored closely and has not increased in size or caused any visual symptoms. The patient has no other medical problems, takes no medications, and does not use tobacco, alcohol, or illicit drugs. She has 3 healthy children and no significant family history. The underlying mechanism for this patient's susceptibility to fracture is most likely to cause which of the following additional manifestations?

A. Hand tremors (5%)

B. Kidney stones (19%)

C. Stomach ulcers (2%)

D. Swallowing difficulty (0%)

✓ E. Vaginal dryness (70%)

Omitted
Correct answer
E

70%
Answered correctly

01 sec
Time Spent

02/21/2020
Last Updated

Explanation

Complications of prolactinoma	
Hyperprolactinemia	• **Premenopausal women:** Galactorrhea, estrogen deficiency (oligo/amenorrhea, decreased bone density, vaginal atrophy) • **Men:** Infertility, decreased libido, impotence

Complications of prolactinoma	
Hyperprolactinemia	• **Premenopausal women:** Galactorrhea, estrogen deficiency (oligo/amenorrhea, decreased bone density, vaginal atrophy) • **Men:** Infertility, decreased libido, impotence • **Children/adolescents:** Delayed puberty, growth impairment
Mass-effect symptoms	• Headache • Visual field defects • Suppression of other pituitary hormones

Prolactinomas are the most common pituitary tumors. High levels of circulating prolactin, a hormone involved in milk production, result in galactorrhea (nonlactational milk production) and infertility in premenopausal women. Excess prolactin suppresses GnRH secretion from the hypothalamus, leading to reduced secretion of LH (and to a lesser extent FSH) and subsequent **hypogonadism**, anovulation, and amenorrhea. The resultant estrogen deficiency can manifest as vasomotor symptoms (eg, hot flashes), **vaginal dryness** and atrophy, and dyspareunia. Because estrogen maintains bone mass in premenopausal women, prolonged estrogen deficiency can lead to **osteoporosis** and an increased risk for fragility fractures (ie, fractures due to minimal trauma, such as a fall from standing height).

Men with prolactinomas may develop symptoms due to hypogonadism (eg, infertility, decreased libido), but galactorrhea is rare in both men and postmenopausal women as milk production requires estrogen/progesterone priming of the breast tissue. Men with prolactinomas are more likely to present at an advanced stage with **mass-effect symptoms** (eg, headache, visual field defects) due to compression of surrounding structures.

(Choices A and D) Central hyperthyroidism due to a TSH-secreting (thyrotroph) pituitary adenoma can present with weight loss, palpitations, systolic hypertension, and hyperadrenergic symptoms (eg, hand tremor). Chronic TSH stimulation can also lead to enlargement of the thyroid gland and compressive symptoms (eg, dysphagia). However, compression of thyrotroph cells by an enlarging prolactinoma causes central hypothyroidism.

(Choices B and C) Multiple endocrine neoplasia type 1 (MEN1) is characterized by primary hyperparathyroidism (with hypercalcemia), pituitary tumors (including prolactinoma), and endocrine pancreatic tumors. Complications of hyperparathyroidism include osteoporosis and kidney stones. Stomach ulcers can occur in MEN1 due to hypercalcemia or a gastrin-producing pancreatic tumor (Zollinger-Ellison syndrome). However,

	• Suppression of other pituitary hormones

Prolactinomas are the most common pituitary tumors. High levels of circulating prolactin, a hormone involved in milk production, result in galactorrhea (nonlactational milk production) and infertility in premenopausal women. Excess prolactin suppresses GnRH secretion from the hypothalamus, leading to reduced secretion of LH (and to a lesser extent FSH) and subsequent **hypogonadism**, anovulation, and amenorrhea. The resultant estrogen deficiency can manifest as vasomotor symptoms (eg, hot flashes), **vaginal dryness** and atrophy, and dyspareunia. Because estrogen maintains bone mass in premenopausal women, prolonged estrogen deficiency can lead to **osteoporosis** and an increased risk for fragility fractures (ie, fractures due to minimal trauma, such as a fall from standing height).

Men with prolactinomas may develop symptoms due to hypogonadism (eg, infertility, decreased libido), but galactorrhea is rare in both men and postmenopausal women as milk production requires estrogen/progesterone priming of the breast tissue. Men with prolactinomas are more likely to present at an advanced stage with **mass-effect symptoms** (eg, headache, visual field defects) due to compression of surrounding structures.

(Choices A and D) Central hyperthyroidism due to a TSH-secreting (thyrotroph) pituitary adenoma can present with weight loss, palpitations, systolic hypertension, and hyperadrenergic symptoms (eg, hand tremor). Chronic TSH stimulation can also lead to enlargement of the thyroid gland and compressive symptoms (eg, dysphagia). However, compression of thyrotroph cells by an enlarging prolactinoma causes central hypothyroidism.

(Choices B and C) Multiple endocrine neoplasia type 1 (MEN1) is characterized by primary hyperparathyroidism (with hypercalcemia), pituitary tumors (including prolactinoma), and endocrine pancreatic tumors. Complications of hyperparathyroidism include osteoporosis and kidney stones. Stomach ulcers can occur in MEN1 due to hypercalcemia or a gastrin-producing pancreatic tumor (Zollinger-Ellison syndrome). However, most prolactinomas are sporadic and not associated with MEN1. In addition, MEN1 is rare, and this patient's lack of a significant family history makes it even less likely.

Educational objective:
In patients with prolactinoma, high levels of circulating prolactin suppress GnRH secretion from the hypothalamus, leading to reduced secretion of LH and subsequent hypogonadism, anovulation, and amenorrhea. The resulting estrogen deficiency can cause osteoporosis with an increased risk for fragility fractures, and lead to vaginal dryness and atrophy.

References

• Hyperprolactinemia: pathophysiology and therapeutic approach.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31

Because estrogen maintains bone mass in premenopausal women, prolonged estrogen deficiency can lead to **osteoporosis** and an increased risk for fragility fractures (ie, fractures due to minimal trauma, such as a fall from standing height).

Men with prolactinomas may develop symptoms due to hypogonadism (eg, infertility, decreased libido), but galactorrhea is rare in both men and postmenopausal women as milk production requires estrogen/progesterone priming of the breast tissue. Men with prolactinomas are more likely to present at an advanced stage with **mass-effect symptoms** (eg, headache, visual field defects) due to compression of surrounding structures.

(Choices A and D) Central hyperthyroidism due to a TSH-secreting (thyrotroph) pituitary adenoma can present with weight loss, palpitations, systolic hypertension, and hyperadrenergic symptoms (eg, hand tremor). Chronic TSH stimulation can also lead to enlargement of the thyroid gland and compressive symptoms (eg, dysphagia). However, compression of thyrotroph cells by an enlarging prolactinoma causes central hypothyroidism.

(Choices B and C) Multiple endocrine neoplasia type 1 (MEN1) is characterized by primary hyperparathyroidism (with hypercalcemia), pituitary tumors (including prolactinoma), and endocrine pancreatic tumors. Complications of hyperparathyroidism include osteoporosis and kidney stones. Stomach ulcers can occur in MEN1 due to hypercalcemia or a gastrin-producing pancreatic tumor (Zollinger-Ellison syndrome). However, most prolactinomas are sporadic and not associated with MEN1. In addition, MEN1 is rare, and this patient's lack of a significant family history makes it even less likely.

Educational objective:
In patients with prolactinoma, high levels of circulating prolactin suppress GnRH secretion from the hypothalamus, leading to reduced secretion of LH and subsequent hypogonadism, anovulation, and amenorrhea. The resulting estrogen deficiency can cause osteoporosis with an increased risk for fragility fractures, and lead to vaginal dryness and atrophy.

References

- Hyperprolactinemia: pathophysiology and therapeutic approach.

Pathophysiology	Endocrine, Diabetes & Metabolism	Pituitary adenoma
Subject	System	Topic

Copyright © UWorld. All rights reserved.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31

A 44-year-old man comes to the clinic due to increasing fatigue, trouble sleeping, and palpitations. He has lost 9 kg (20 lb) over the last year despite eating well. The patient says he is under a lot of pressure at work but cannot think of any other precipitating factors for his insomnia. He has no other medical problems and takes no medications. The patient does not use tobacco, alcohol, or illicit drugs. His mother has a history of a thyroid problem. Blood pressure is 140/80 mm Hg and pulse is 108/min. On physical examination, the thyroid is diffusely enlarged. His serum free thyroxine level is elevated and TSH level is decreased. He is found to have a positive assay for thyrotropin receptor antibodies. If present, which of the following additional findings would be most specific to the underlying cause of this patient's hyperthyroidism?

A. Atrial fibrillation

B. Decreased bone mineral density

C. Heat intolerance

D. Skin thickening and induration over the shin

E. Tremor of the outstretched hands

Submit

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31

A 44-year-old man comes to the clinic due to increasing fatigue, trouble sleeping, and palpitations. He has lost 9 kg (20 lb) over the last year despite eating well. The patient says he is under a lot of pressure at work but cannot think of any other precipitating factors for his insomnia. He has no other medical problems and takes no medications. The patient does not use tobacco, alcohol, or illicit drugs. His mother has a history of a thyroid problem. Blood pressure is 140/80 mm Hg and pulse is 108/min. On physical examination, the thyroid is diffusely enlarged. His serum free thyroxine level is elevated and TSH level is decreased. He is found to have a positive assay for thyrotropin receptor antibodies. If present, which of the following additional findings would be most specific to the underlying cause of this patient's hyperthyroidism?

A. Atrial fibrillation (4%)

B. Decreased bone mineral density (4%)

C. Heat intolerance (27%)

✓ D. Skin thickening and induration over the shin (58%)

E. Tremor of the outstretched hands (5%)

Omitted
Correct answer
D

58%
Answered correctly

02 secs
Time Spent

03/15/2020
Last Updated

Explanation

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31

A 44-year-old man comes to the clinic due to increasing fatigue, trouble sleeping, and palpitations. He has lost 9 kg (20 lb) over the last year despite eating well. The patient says he is under a lot of pressure at work but cannot think of any other precipitating factors for his insomnia. He has no other medical problems and takes no medications. The patient does not use tobacco, alcohol, or illicit drugs. His mother has a history of a thyroid problem. Blood pressure is 140/80 mm Hg and pulse is 108/min. On physical examination, the thyroid is diffusely enlarged. His serum free thyroxine level is elevated and TSH level is decreased. He is found to have a positive assay for thyrotropin receptor antibodies. If present, which of the following additional findings would be most specific to the underlying cause of this patient's hyperthyroidism?

- A. Atrial fibrillation (4%)
- B. Decreased bone mineral density (4%)
- C. Heat intolerance (27%)
- ✓ D. Skin thickening and induration over the shin (58%)
- E. Tremor of the outstretched hands (5%)

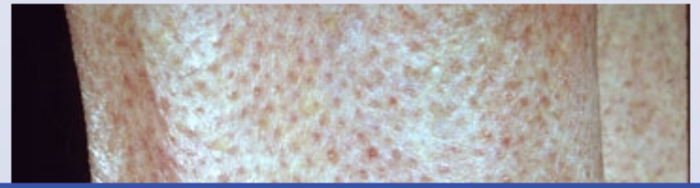
Omitted
Correct answer
D

58%
Answered correctly

02 secs
Time Spent

03/15/2020
Last Updated

Explanation



1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31

This patient has symptomatic hyperthyroidism with elevated serum free thyroxine and suppressed TSH levels. The most common cause of hyperthyroidism is **Graves disease**, however, hyperthyroidism can also be due to other processes such as toxic adenoma, toxic multinodular goiter, and thyroiditis. This patient's positive serum assay for **thyrotropin receptor antibodies** (TRAb) confirms the diagnosis of Graves disease. TRAb bind and activate the TSH receptor, causing increased release of thyroid hormone by the thyroid gland, which is responsible for the general symptoms of hyperthyroidism (eg, fatigue, palpitations, weight loss, and insomnia).

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31

This patient has symptomatic hyperthyroidism with elevated serum free thyroxine and suppressed TSH levels. The most common cause of hyperthyroidism is **Graves disease**, however, hyperthyroidism can also be due to other processes such as toxic adenoma, toxic multinodular goiter, and thyroiditis. This patient's positive serum assay for **thyrotropin receptor antibodies** (TRAb) confirms the diagnosis of Graves disease. TRAb bind and activate the TSH receptor, causing increased release of thyroid hormone by the thyroid gland, which is responsible for the general symptoms of hyperthyroidism (eg, fatigue, palpitations, weight loss, and insomnia).

In addition to the thyroid, the TSH receptor antigen is present on fibroblasts, adipocytes, and other tissues. **Thyroid dermopathy** is caused by stimulation of fibroblasts by TRAb and activated T-cells, leading to excess production of glycosaminoglycans and adipogenesis. This leads to induration and thickening of the skin over the shins (**pretibial myxedema**, as shown above). Graves ophthalmopathy occurs in a similar manner, with expansion of the retro-orbital tissues displacing the globe forward (proptosis). Because these processes are directly related to TRAb, they have a high specificity for Graves disease.

(Choices A, B, C, and E) Hyperthyroidism also causes a hypermetabolic/hyperadrenergic state that can present with heat intolerance, tremor, lid lag, tachycardia, or atrial fibrillation. In addition, increased bone turnover can lead to osteoporosis and increased fracture risk. However, these findings are not mediated by TRAb and can be seen in hyperthyroidism of any cause (eg, thyroiditis, toxic multinodular goiter).

Educational objective:
Pretibial myxedema and Graves ophthalmopathy are specific features of Graves disease. They are caused by an autoimmune response directed against the TSH receptor that results in the accumulation of glycosaminoglycans within the affected tissues.

References

- Thyroid dermopathy and acropachy.

Pathophysiology	Endocrine, Diabetes & Metabolism	Hyperthyroidism
Subject	System	Topic

Copyright © UWorld. All rights reserved.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31

Exhibit Display

Zoom In | Zoom Out | Reset | Add To New Card | Existing Card

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31

A 65-year-old man with benign prostatic hyperplasia comes to the office for a follow-up appointment. He has a history of obstructive urinary symptoms that were unrelieved with tamsulosin, and a new medication was prescribed at his last visit 8 months ago. Since starting the new medication, the patient has experienced gradual improvement in urinary hesitancy and strength of urinary stream. However, he also has noticed a significant increase in the size of his breasts. The patient reports no pain or changes in weight. Glandular tissue, approximately 2 cm in diameter, is palpated under the nipples and is mildly tender to palpation. There is no nipple discharge, breast asymmetry, or rash. This patient's breast findings are most likely due to which of the following effects?

A. Blockade of androgen receptors

B. Decreased testicular production of testosterone

C. Displacement of estrogen from sex hormone–binding globulin

D. Increased peripheral conversion of testosterone to estrone

E. Increased prolactin production

Submit

A 65-year-old man with benign prostatic hyperplasia comes to the office for a follow-up appointment. He has a history of obstructive urinary symptoms that were unrelieved with tamsulosin, and a new medication was prescribed at his last visit 8 months ago. Since starting the new medication, the patient has experienced gradual improvement in urinary hesitancy and strength of urinary stream. However, he also has noticed a significant increase in the size of his breasts. The patient reports no pain or changes in weight. Glandular tissue, approximately 2 cm in diameter, is palpated under the nipples and is mildly tender to palpation. There is no nipple discharge, breast asymmetry, or rash. This patient's breast findings are most likely due to which of the following effects?

- A. Blockade of androgen receptors (27%)
- B. Decreased testicular production of testosterone (9%)
- C. Displacement of estrogen from sex hormone–binding globulin (4%)
- ✓ D. Increased peripheral conversion of testosterone to estrone (54%)
- E. Increased prolactin production (3%)

Omitted
Correct answer
D

54%
Answered correctly

03 secs
Time Spent

03/02/2020
Last Updated

Explanation

Gynecomastia	
Clinical findings	• Development of glandular breast tissue in males
	• Increased estrogen/androgen ratio

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31

Gynecomastia	
Clinical findings	• Development of glandular breast tissue in males
Pathophysiology	• Increased estrogen/androgen ratio • Ductal epithelial hyperplasia & stromal fibrosis

Common etiologies	• Increased estrogen levels (eg, cirrhosis, obesity)
	• Decreased testosterone levels (eg, chronic kidney disease, hypogonadism)
	• Medication effect
	  ◦ Decreased androgen production (eg, GnRH agonists, ketoconazole)
	  ◦ Decreased conversion to dihydrotestosterone (eg, 5-alpha reductase inhibitors)
	  ◦ Inhibition of androgen receptors (eg, spironolactone, bicalutamide)

Gynecomastia is the abnormal development of glandular breast tissue in males. It is characterized by ductal epithelial hyperplasia with fibrosis of the surrounding stroma. Breast growth is inhibited by androgens and promoted by estrogens; conditions that cause **increased estrogen/androgen ratio** can lead to gynecomastia.

This patient, who failed first-line therapy for benign prostatic hyperplasia, has likely been prescribed a **5-alpha reductase inhibitor** (eg, finasteride, dutasteride). These medications **block conversion of testosterone to dihydrotestosterone** (which has a higher affinity for the testosterone receptor and mediates the majority of testosterone effects); the **excess testosterone** is then **converted to estrogens** (eg, estrone) by aromatase, leading to gynecomastia. Both the beneficial effects and potential gynecomastia develop slowly and are generally not apparent in the first several months of therapy with 5-alpha reductase inhibitors.

(Choice A) Cimetidine, spironolactone, and antiandrogens (eg, flutamide, bicalutamide) block the binding of androgens to receptors in target tissues.

(Choice B) Ketoconazole inhibits a number of enzymes in the steroid hormone biosynthetic pathway, and prolonged use can cause gynecomastia due to deficient testosterone synthesis. Long-acting GnRH analogues (eg, leuprolide) suppress LH secretion and also decrease testicular testosterone production (in contrast with endogenous [pulsatile] GnRH secretion).

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31

Gynecomastia	
Clinical findings	• Development of glandular breast tissue in males
Pathophysiology	• Increased estrogen/androgen ratio • Ductal epithelial hyperplasia & stromal fibrosis

Common etiologies	• Increased estrogen levels (eg, cirrhosis, obesity)
	• Decreased testosterone levels (eg, chronic kidney disease, hypogonadism)
	• Medication effect
	  ◦ Decreased androgen production (eg, GnRH agonists, ketoconazole)
	  ◦ Decreased conversion to dihydrotestosterone (eg, 5-alpha reductase inhibitors)
	  ◦ Inhibition of androgen receptors (eg, spironolactone, bicalutamide)

Gynecomastia is the abnormal development of glandular breast tissue in males. It is characterized by ductal epithelial hyperplasia with fibrosis of the surrounding stroma. Breast growth is inhibited by androgens and promoted by estrogens; conditions that cause **increased estrogen/androgen ratio** can lead to gynecomastia.

This patient, who failed first-line therapy for benign prostatic hyperplasia, has likely been prescribed a **5-alpha reductase inhibitor** (eg, finasteride, dutasteride). These medications **block conversion of testosterone to dihydrotestosterone** (which has a higher affinity for the testosterone receptor and mediates the majority of testosterone effects); the **excess testosterone** is then **converted to estrogens** (eg, estrone) by aromatase, leading to gynecomastia. Both the beneficial effects and potential gynecomastia develop slowly and are generally not apparent in the first several months of therapy with 5-alpha reductase inhibitors.

(Choice A) Cimetidine, spironolactone, and antiandrogens (eg, flutamide, bicalutamide) block the binding of androgens to receptors in target tissues.

(Choice B) Ketoconazole inhibits a number of enzymes in the steroid hormone biosynthetic pathway, and prolonged use can cause gynecomastia due to deficient testosterone synthesis. Long-acting GnRH analogues (eg, leuprolide) suppress LH secretion and also decrease testicular testosterone production (in contrast with endogenous [pulsatile] GnRH secretion).

Gynecomastia is the abnormal development of glandular breast tissue in males. It is characterized by ductal epithelial hyperplasia with fibrosis of the surrounding stroma. Breast growth is inhibited by androgens and promoted by estrogens; conditions that cause **increased estrogen/androgen ratio** can lead to gynecomastia.

This patient, who failed first-line therapy for benign prostatic hyperplasia, has likely been prescribed a **5-alpha reductase inhibitor** (eg, finasteride, dutasteride). These medications **block conversion of testosterone to dihydrotestosterone** (which has a higher affinity for the testosterone receptor and mediates the majority of testosterone effects); the **excess testosterone** is then **converted to estrogens** (eg, estrone) by aromatase, leading to gynecomastia. Both the beneficial effects and potential gynecomastia develop slowly and are generally not apparent in the first several months of therapy with 5-alpha reductase inhibitors.

(Choice A) Cimetidine, spironolactone, and antiandrogens (eg, flutamide, bicalutamide) block the binding of androgens to receptors in target tissues.

(Choice B) Ketoconazole inhibits a number of enzymes in the steroid hormone biosynthetic pathway, and prolonged use can cause gynecomastia due to deficient testosterone synthesis. Long-acting GnRH analogues (eg, leuprolide) suppress LH secretion and also decrease testicular testosterone production (in contrast with endogenous [pulsatile] GnRH secretion).

(Choice C) Multiple medications, including spironolactone and ketoconazole, can displace estrogen from plasma binding proteins and raise free estrogen levels.

(Choice E) Pituitary prolactin secretion is under negative regulation by dopamine. Dopamine receptor antagonists (eg, antipsychotic medications) facilitate increased prolactin release and can cause a sense of fullness in the breasts and occasionally galactorrhea.

Educational objective:
5-Alpha reductase inhibitors (eg, finasteride, dutasteride) are used in the treatment of benign prostatic hyperplasia. These medications block the conversion of testosterone to dihydrotestosterone; the excess testosterone is then available for conversion to estrogens (eg, estradiol) by aromatase, which can lead to gynecomastia.

References

- Risk of gynecomastia and breast cancer associated with the use of 5-alpha reductase inhibitors for benign prostatic hyperplasia.

Pathophysiology Endocrine, Diabetes & Metabolism Gynecomastia

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31

estrogen/androgen ratio can lead to gynecomastia.

This patient, who failed first-line therapy for benign prostatic hyperplasia, has likely been prescribed a **5-alpha reductase inhibitor** (eg, finasteride, dutasteride). These medications **block conversion of testosterone to dihydrotestosterone** (which has a higher affinity for the testosterone receptor and mediates the majority of testosterone effects); the **excess testosterone** is then **converted to estrogens** (eg, estrone) by aromatase, leading to gynecomastia. Both the beneficial effects and potential gynecomastia develop slowly and are generally not apparent in the first several months of therapy with 5-alpha reductase inhibitors.

(Choice A) Cimetidine, spironolactone, and antiandrogens (eg, flutamide, bicalutamide) block the binding of androgens to receptors in target tissues.

(Choice B) Ketoconazole inhibits a number of enzymes in the steroid hormone biosynthetic pathway, and prolonged use can cause gynecomastia due to deficient testosterone synthesis. Long-acting GnRH analogues (eg, leuprolide) suppress LH secretion and also decrease testicular testosterone production (in contrast with endogenous [pulsatile] GnRH secretion).

(Choice C) Multiple medications, including spironolactone and ketoconazole, can displace estrogen from plasma binding proteins and raise free estrogen levels.

(Choice E) Pituitary prolactin secretion is under negative regulation by dopamine. Dopamine receptor antagonists (eg, antipsychotic medications) facilitate increased prolactin release and can cause a sense of fullness in the breasts and occasionally galactorrhea.

Educational objective:
5-Alpha reductase inhibitors (eg, finasteride, dutasteride) are used in the treatment of benign prostatic hyperplasia. These medications block the conversion of testosterone to dihydrotestosterone; the excess testosterone is then available for conversion to estrogens (eg, estradiol) by aromatase, which can lead to gynecomastia.

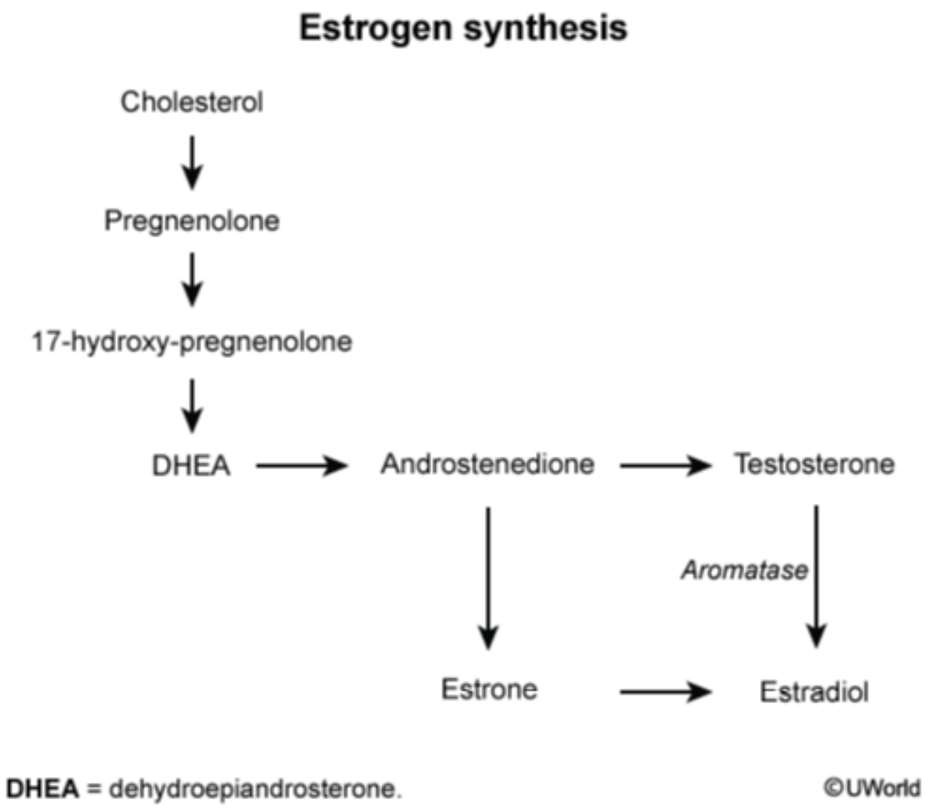
References

- Risk of gynecomastia and breast cancer associated with the use of 5-alpha reductase inhibitors for benign prostatic hyperplasia.

Pathophysiology	Endocrine, Diabetes & Metabolism	Gynecomastia
Subject	System	Topic

This patient, who failed first-line therapy for benign prostatic hyperplasia, has likely been prescribed a **5-alpha reductase inhibitor** (eg,

Exhibit Display



Zoom In | Zoom Out | Reset | Add To New Card | Existing Card

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31

A 58-year-old man is hospitalized due to sudden onset of chest pain. Blood pressure is 160/110 mm Hg and pulse is 90/min. BMI is 26.9 kg/m^2. A baseline ECG shows nonspecific ST-segment and T-wave abnormalities, and serial troponin measurements are normal. The patient's fasting plasma glucose level is 160 mg/dL, although he has not been diagnosed previously with diabetes mellitus. Serum triglyceride level is elevated, and the HDL level is low. Which of the following additional findings would be most suggestive of increased insulin resistance in this patient?

A. Decreased hepatic glucose production

B. Elevated LDL level

C. High urine ketone concentration

D. Increased glycogen stores in skeletal muscles

E. Increased waist circumference

Submit

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31

A 58-year-old man is hospitalized due to sudden onset of chest pain. Blood pressure is 160/110 mm Hg and pulse is 90/min. BMI is 26.9 kg/m^2. A baseline ECG shows nonspecific ST-segment and T-wave abnormalities, and serial troponin measurements are normal. The patient's fasting plasma glucose level is 160 mg/dL, although he has not been diagnosed previously with diabetes mellitus. Serum triglyceride level is elevated, and the HDL level is low. Which of the following additional findings would be most suggestive of increased insulin resistance in this patient?

- A. Decreased hepatic glucose production (4%)
- B. Elevated LDL level (12%)
- C. High urine ketone concentration (17%)
- D. Increased glycogen stores in skeletal muscles (2%)
- ✓ E. Increased waist circumference (62%)

Omitted
Correct answer
E

62%
Answered correctly

03 secs
Time Spent

01/19/2020
Last Updated

Explanation

This patient has hypertension and likely **type 2 diabetes mellitus**. The primary defects in the pathophysiology of type 2 diabetes include **defective insulin secretion** from pancreatic beta cells and **insulin resistance** in peripheral tissues. Insulin resistance is caused by a number of genetic (eg, insulin receptor and postreceptor mutations) and environmental factors (eg, lack of physical activity, obesity).

An adipose body habitus is commonly associated with insulin resistance and type 2 diabetes. In particular, excess **visceral fat** (surrounding internal organs) correlates much more strongly with insulin resistance than does subcutaneous fat. Measurement of **waist circumference** or **waist-to-hip ratio** is an effective indirect assessment of visceral fat, especially in patients who are overweight (BMI 25-29.9 kg/m^2) or mildly obese

This patient has hypertension and likely **type 2 diabetes mellitus**. The primary defects in the pathophysiology of type 2 diabetes include **defective insulin secretion** from pancreatic beta cells and **insulin resistance** in peripheral tissues. Insulin resistance is caused by a number of genetic (eg, insulin receptor and postreceptor mutations) and environmental factors (eg, lack of physical activity, obesity).

An adipose body habitus is commonly associated with insulin resistance and type 2 diabetes. In particular, excess **visceral fat** (surrounding internal organs) correlates much more strongly with insulin resistance than does subcutaneous fat. Measurement of **waist circumference** or **waist-to-hip ratio** is an effective indirect assessment of visceral fat, especially in patients who are overweight (BMI 25-29.9 kg/m^2) or mildly obese (BMI 30-34.9 kg/m^2). A waist circumference >102 cm (40 in) in men and >88 cm (35 in) in women is associated with a higher risk of insulin resistance.

The association of insulin resistance, increased visceral adiposity (ie, increased waist circumference), hypertension, and serum lipid abnormalities (high triglyceride levels, low HDL levels) is known as **metabolic syndrome** (sometimes called syndrome X). Patients with metabolic syndrome have increased rates of **cardiovascular events** and warrant careful risk factor management.

(Choice A) Insulin suppresses gluconeogenesis and promotes glycogen synthesis in the liver. In patients with insulin resistance, the inhibitory effect of insulin on gluconeogenesis is reduced, leading to increased hepatic glucose production.

(Choice B) High LDL levels are an independent risk factor for atherosclerotic heart disease in patients with diabetes, but are not directly associated with increased insulin resistance. In contrast, insulin resistance is associated with high triglyceride and low HDL levels.

(Choice C) High urinary excretion of ketones suggests absolute insulin deficiency, as seen in type 1 diabetes, rather than insulin resistance. Patients with type 2 diabetes and insulin resistance typically have high circulating insulin levels that are more than adequate to suppress ketone formation.

(Choice D) Skeletal muscle is a major repository for ingested glucose due to insulin-mediated glucose uptake. In patients with insulin resistance, decreased glucose uptake in skeletal muscle leads to reduced glycogen synthesis and higher blood glucose levels.

Educational objective:
Visceral obesity as measured by waist circumference or waist-to-hip ratio is an important predictor of insulin resistance.

References

- Abdominal obesity: a marker of ectopic fat accumulation.

resistance.

The association of insulin resistance, increased visceral adiposity (ie, increased waist circumference), hypertension, and serum lipid abnormalities (high triglyceride levels, low HDL levels) is known as **metabolic syndrome** (sometimes called syndrome X). Patients with metabolic syndrome have increased rates of **cardiovascular events** and warrant careful risk factor management.

(Choice A) Insulin suppresses gluconeogenesis and promotes glycogen synthesis in the liver. In patients with insulin resistance, the inhibitory effect of insulin on gluconeogenesis is reduced, leading to increased hepatic glucose production.

(Choice B) High LDL levels are an independent risk factor for atherosclerotic heart disease in patients with diabetes, but are not directly associated with increased insulin resistance. In contrast, insulin resistance is associated with high triglyceride and low HDL levels.

(Choice C) High urinary excretion of ketones suggests absolute insulin deficiency, as seen in type 1 diabetes, rather than insulin resistance. Patients with type 2 diabetes and insulin resistance typically have high circulating insulin levels that are more than adequate to suppress ketone formation.

(Choice D) Skeletal muscle is a major repository for ingested glucose due to insulin-mediated glucose uptake. In patients with insulin resistance, decreased glucose uptake in skeletal muscle leads to reduced glycogen synthesis and higher blood glucose levels.

Educational objective:
Visceral obesity as measured by waist circumference or waist-to-hip ratio is an important predictor of insulin resistance.

References

- Abdominal obesity: a marker of ectopic fat accumulation.
- Low-density-lipoprotein cholesterol concentrations and risk of incident diabetes: epidemiological and genetic insights from the Framingham Heart Study.

Pathophysiology	Endocrine, Diabetes & Metabolism	Metabolic syndrome
Subject	System	Topic

Copyright © UWorld. All rights reserved.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31

A 50-year-old female presents with abdominal pain, diarrhea, and weight loss. She was diagnosed with diabetes mellitus two months ago. Her serum somatostatin level is highly elevated. Further evaluation reveals biliary stones. Suppression of which of the following hormones is most likely responsible for biliary stones?

- A. Secretin
- B. Cholecystokinin
- C. Glucagon
- D. Insulin
- E. Gastrin
- F. Growth hormone

Submit

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31

A 50-year-old female presents with abdominal pain, diarrhea, and weight loss. She was diagnosed with diabetes mellitus two months ago. Her serum somatostatin level is highly elevated. Further evaluation reveals biliary stones. Suppression of which of the following hormones is most likely responsible for biliary stones?

- A. Secretin (4%)
- ✓ B. Cholecystokinin (87%)
- C. Glucagon (2%)
- D. Insulin (2%)
- E. Gastrin (2%)
- F. Growth hormone (2%)

Omitted
Correct answer
B

87%
Answered correctly

02 secs
Time Spent

02/03/2020
Last Updated

Explanation

The term somatostatin was originally applied to the 14-aminoacid cyclic peptide that is secreted by the hypothalamus and that inhibits the production of growth hormone from the anterior pituitary gland. Somatostatin is now known to be secreted from other parts of the central nervous system and from pancreatic delta cells. Somatostatin secreted from pancreatic "delta cells" decreases the secretion of secretin, cholecystokinin, glucagon, insulin, and gastrin. Somatostatinomas are rare pancreatic islet cell tumors that arise from delta cells. Patients with somatostatinomas present with hyperglycemia or hypoglycemia, steatorrhea (excessive fat in the feces), and gallbladder stones. Gallbladder stones form because of

B

Answered correctly
Time Spent
Last Updated

Explanation

The term somatostatin was originally applied to the 14-aminoacid cyclic peptide that is secreted by the hypothalamus and that inhibits the production of growth hormone from the anterior pituitary gland. Somatostatin is now known to be secreted from other parts of the central nervous system and from pancreatic delta cells. Somatostatin secreted from pancreatic "delta cells" decreases the secretion of secretin, cholecystokinin, glucagon, insulin, and gastrin. Somatostatinomas are rare pancreatic islet cell tumors that arise from delta cells. Patients with somatostatinomas present with hyperglycemia or hypoglycemia, steatorrhea (excessive fat in the feces), and gallbladder stones. Gallbladder stones form because of poor gallbladder contractility, which is secondary to inhibition of cholecystokinin release.

(Choices C and D) Somatostatin decreases the release of glucagon as well as insulin. However, the secretion of insulin is more profoundly inhibited than is glucagon; therefore, the net result is hyperglycemia.

(Choice A) Steatorrhea results from the decreased secretion of secretin as well as a decrease in gastrointestinal motility.

(Choice E) A decrease in gastrin release causes hypochlorhydria.

(Choice F) As indicated above, somatostatin does decrease growth hormone secretion from the normal pituitary gland, and it does so in growth-hormone-secreting pituitary adenomas. However, somatostatin cannot be used in clinical practice because of its extremely short half-life. Somatostatin analogs (octreotide and lanreotide) have a longer plasma half-life and are available for clinical use.

Educational Objective:
Reduced gallbladder contractility, due to decreased cholecystokinin secretion, is responsible for biliary stones in patients with somatostatinoma.

Pathophysiology	Endocrine, Diabetes & Metabolism	Gastrointestinal hormones
Subject	System	Topic

Copyright © UWorld. All rights reserved.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31

A 27-year-old man comes to the office due to recurrent episodes of muscle weakness. He has no other significant past medical history. The patient's weight has been stable for the past few years, and his current BMI is 23 kg/m^2. His blood pressure is 190/110 mm Hg supine and 195/110 mm Hg standing. His heart rate is 70/min supine and 72/min standing. The rest of the physical examination is unremarkable. Laboratory evaluation shows very low plasma renin activity. Overactivity of which of the following structures is most likely responsible for this patient's symptoms?

A. Chromaffin cells of the adrenals
B. Extra-adrenal paraganglion cells
C. Juxtaglomerular cells of the kidney
D. Zona fasciculata of the adrenals
E. Zona glomerulosa of the adrenals
F. Zona reticularis of the adrenals

Submit

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31

A 27-year-old man comes to the office due to recurrent episodes of muscle weakness. He has no other significant past medical history. The patient's weight has been stable for the past few years, and his current BMI is 23 kg/m^2. His blood pressure is 190/110 mm Hg supine and 195/110 mm Hg standing. His heart rate is 70/min supine and 72/min standing. The rest of the physical examination is unremarkable. Laboratory evaluation shows very low plasma renin activity. Overactivity of which of the following structures is most likely responsible for this patient's symptoms?

- A. Chromaffin cells of the adrenals (9%)
- B. Extra-adrenal paraganglion cells (0%)
- C. Juxtaglomerular cells of the kidney (4%)
- D. Zona fasciculata of the adrenals (5%)
- ✓ E. Zona glomerulosa of the adrenals (78%)
- F. Zona reticularis of the adrenals (0%)

Omitted
Correct answer
E

78%
Answered correctly

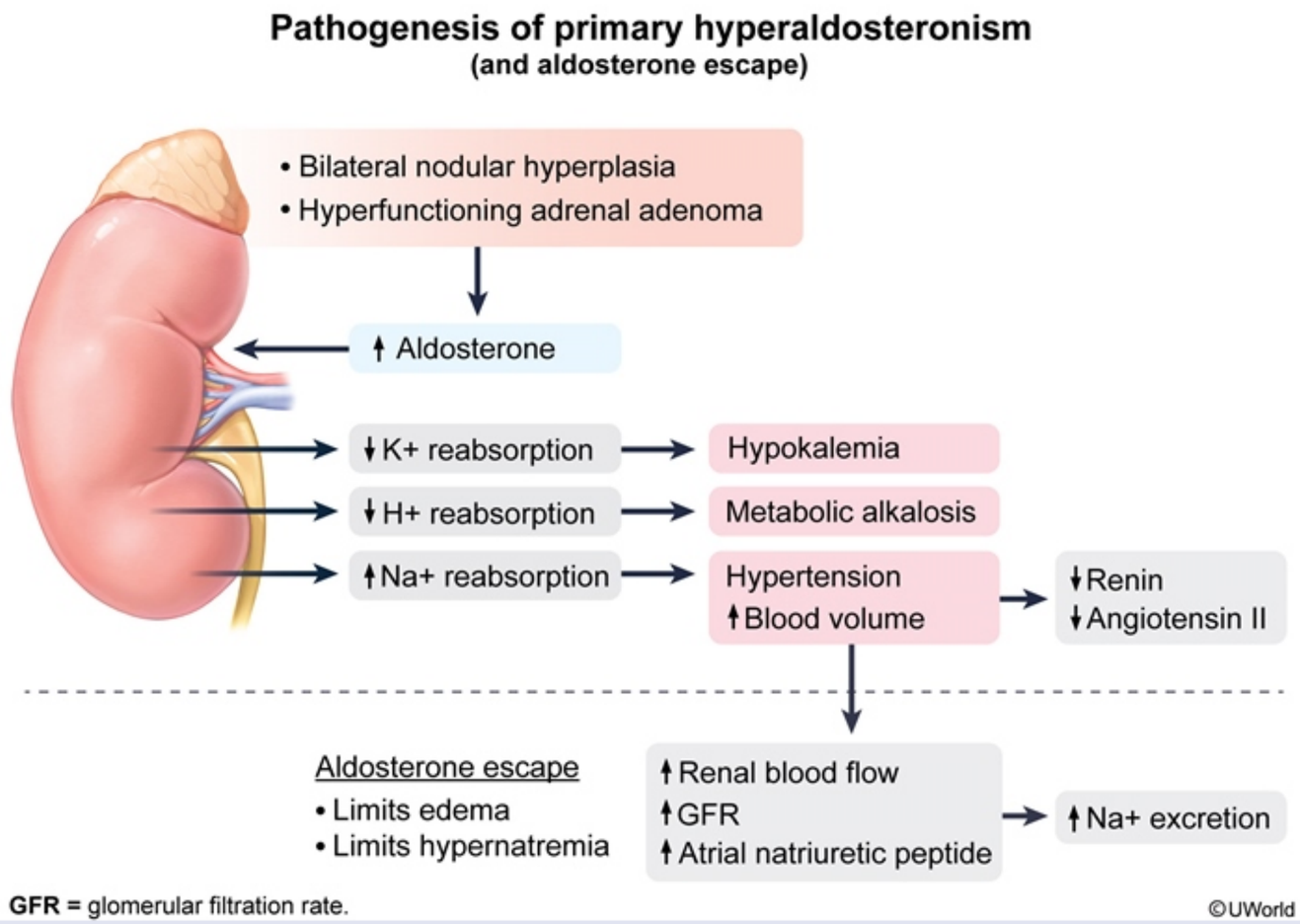
02 secs
Time Spent

01/30/2020
Last Updated

Explanation

Pathogenesis of primary hyperaldosteronism
(and aldosterone escape)

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31



This patient has features consistent with **primary hyperaldosteronism (PH)**, a very common cause of secondary hypertension. PH is usually due to increased secretion of mineralocorticoids from bilateral nodular hyperplasia of the adrenal zona glomerulosa or an aldosterone-producing adrenal adenoma (Conn syndrome).

The main effect of aldosterone is to stimulate absorption of sodium and excretion of potassium and hydrogen ions in the renal collecting tubules. Aldosterone secretion from the zona glomerulosa is normally regulated by angiotensin II and potassium levels. Overproduction of aldosterone can

GFR = glomerular filtration rate.

©UWorld

This patient has features consistent with **primary hyperaldosteronism (PH)**, a very common cause of secondary hypertension. PH is usually due to increased secretion of mineralocorticoids from bilateral nodular hyperplasia of the adrenal zona glomerulosa or an aldosterone-producing adrenal adenoma (Conn syndrome).

The main effect of aldosterone is to stimulate absorption of sodium and excretion of potassium and hydrogen ions in the renal collecting tubules. Aldosterone secretion from the zona glomerulosa is normally regulated by angiotensin II and potassium levels. Overproduction of aldosterone can result in sodium retention, **hypertension**, and feedback suppression of the renin-angiotensin system (ie, **very low renin activity**). Some patients also develop metabolic alkalosis and **hypokalemia**, which can be exacerbated by increased distal tubule sodium delivery (eg, diuretics, increased sodium intake). Symptomatic hypokalemia may cause **muscle weakness**, cramps, and, occasionally, rhabdomyolysis and cardiac arrhythmias.

Despite the increase in sodium absorption, hypernatremia and pedal edema are rarely observed in PH due to the phenomenon of **aldosterone escape**. The high aldosterone levels lead to increased intravascular volume and therefore cause increased renal blood flow (with resulting pressure natriuresis) and augmented release of atrial natriuretic peptide. This ultimately results in increased sodium excretion by the renal tubules, which limits net sodium retention and prevents the development of overt volume overload and significant hypernatremia.

(Choices A and B) Pheochromocytomas are catecholamine-secreting tumors arising from the chromaffin cells of the adrenal medulla or extra-adrenal sympathetic chain, and typically present with severe hypertension. Pheochromocytomas stimulate the renin-angiotensin system due to high circulating catecholamine levels, and are associated with tachycardia and symptoms of catecholamine excess (eg, sweating, palpitations, headache).

(Choice C) Increased renin production by the juxtaglomerular apparatus leads to hypertension with elevated aldosterone levels. This typically occurs in the setting of renal artery stenosis with decreased renal blood flow. However, this patient's renin activity is suppressed.

(Choices D and F) Hypersecretion from cells of the zona fasciculata or zona reticularis would lead to Cushing syndrome or hyperandrogenism, respectively. Cushing syndrome can cause hypertension and hypokalemia but is usually associated with weight gain and a Cushingoid body habitus (eg, central obesity, moon facies).

Educational objective:
Primary hyperaldosteronism is caused by excessive aldosterone secretion, typically as a result of bilateral nodular hyperplasia of the zona glomerulosa or an aldosterone-producing adrenal adenoma. Clinical findings include hypertension, low plasma renin activity, hypokalemia, and

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31

sodium intake). Symptomatic hypokalemia may cause **muscle weakness**, cramps, and, occasionally, rhabdomyolysis and cardiac arrhythmias.

Despite the increase in sodium absorption, hypernatremia and pedal edema are rarely observed in PH due to the phenomenon of **aldosterone escape**. The high aldosterone levels lead to increased intravascular volume and therefore cause increased renal blood flow (with resulting pressure natriuresis) and augmented release of atrial natriuretic peptide. This ultimately results in increased sodium excretion by the renal tubules, which limits net sodium retention and prevents the development of overt volume overload and significant hypernatremia.

(Choices A and B) Pheochromocytomas are catecholamine-secreting tumors arising from the chromaffin cells of the adrenal medulla or extra-adrenal sympathetic chain, and typically present with severe hypertension. Pheochromocytomas stimulate the renin-angiotensin system due to high circulating catecholamine levels, and are associated with tachycardia and symptoms of catecholamine excess (eg, sweating, palpitations, headache).

(Choice C) Increased renin production by the juxtaglomerular apparatus leads to hypertension with elevated aldosterone levels. This typically occurs in the setting of renal artery stenosis with decreased renal blood flow. However, this patient's renin activity is suppressed.

(Choices D and F) Hypersecretion from cells of the zona fasciculata or zona reticularis would lead to Cushing syndrome or hyperandrogenism, respectively. Cushing syndrome can cause hypertension and hypokalemia but is usually associated with weight gain and a Cushingoid body habitus (eg, central obesity, moon facies).

Educational objective:
Primary hyperaldosteronism is caused by excessive aldosterone secretion, typically as a result of bilateral nodular hyperplasia of the zona glomerulosa or an aldosterone-producing adrenal adenoma. Clinical findings include hypertension, low plasma renin activity, hypokalemia, and metabolic alkalosis.

References

- Case detection, diagnosis, and treatment of patients with primary aldosteronism: an endocrine society clinical practice guideline

Pathophysiology	Endocrine, Diabetes & Metabolism	Hyperaldosteronism
Subject	System	Topic

Copyright © UWorld. All rights reserved.

A 30-year-old woman is evaluated for a 3-month history of progressive fatigue, decreased appetite, and 10-lb (4.5-kg) weight loss. The patient has type 1 diabetes mellitus and has noticed decreased insulin requirements over this time. She has no other medical conditions and does not use tobacco, alcohol, or illicit drugs. Physical examination shows a generalized increase in pigmentation of the skin, especially involving the palmar creases. Measurement of serum cortisol before and after administration of exogenous adrenocorticotropic hormone (ACTH) shows no difference in the levels. Which of the following changes in serum laboratory values is most likely present in this patient?

	Sodium	Potassium	Chloride	Bicarbonate
A.	Normal	↓	↓	↑
B.	↓	↑	↑	↓
C.	↓	↓	↓	↑
D.	Normal	↑	Normal	Normal
E.	Normal	↓	↑	↓

Submit

A 30-year-old woman is evaluated for a 3-month history of progressive fatigue, decreased appetite, and 10-lb (4.5-kg) weight loss. The patient has type 1 diabetes mellitus and has noticed decreased insulin requirements over this time. She has no other medical conditions and does not use tobacco, alcohol, or illicit drugs. Physical examination shows a generalized increase in pigmentation of the skin, especially involving the palmar creases. Measurement of serum cortisol before and after administration of exogenous adrenocorticotropic hormone (ACTH) shows no difference in the levels. Which of the following changes in serum laboratory values is most likely present in this patient?

	Sodium	Potassium	Chloride	Bicarbonate
A. (16%)	Normal	↓	↓	↑
✓ B. (51%)	↓	↑	↑	↓
C. (7%)	↓	↓	↓	↑
D. (13%)	Normal	↑	Normal	Normal
E. (10%)	Normal	↓	↑	↓

Omitted
Correct answer
B

51%
Answered correctly

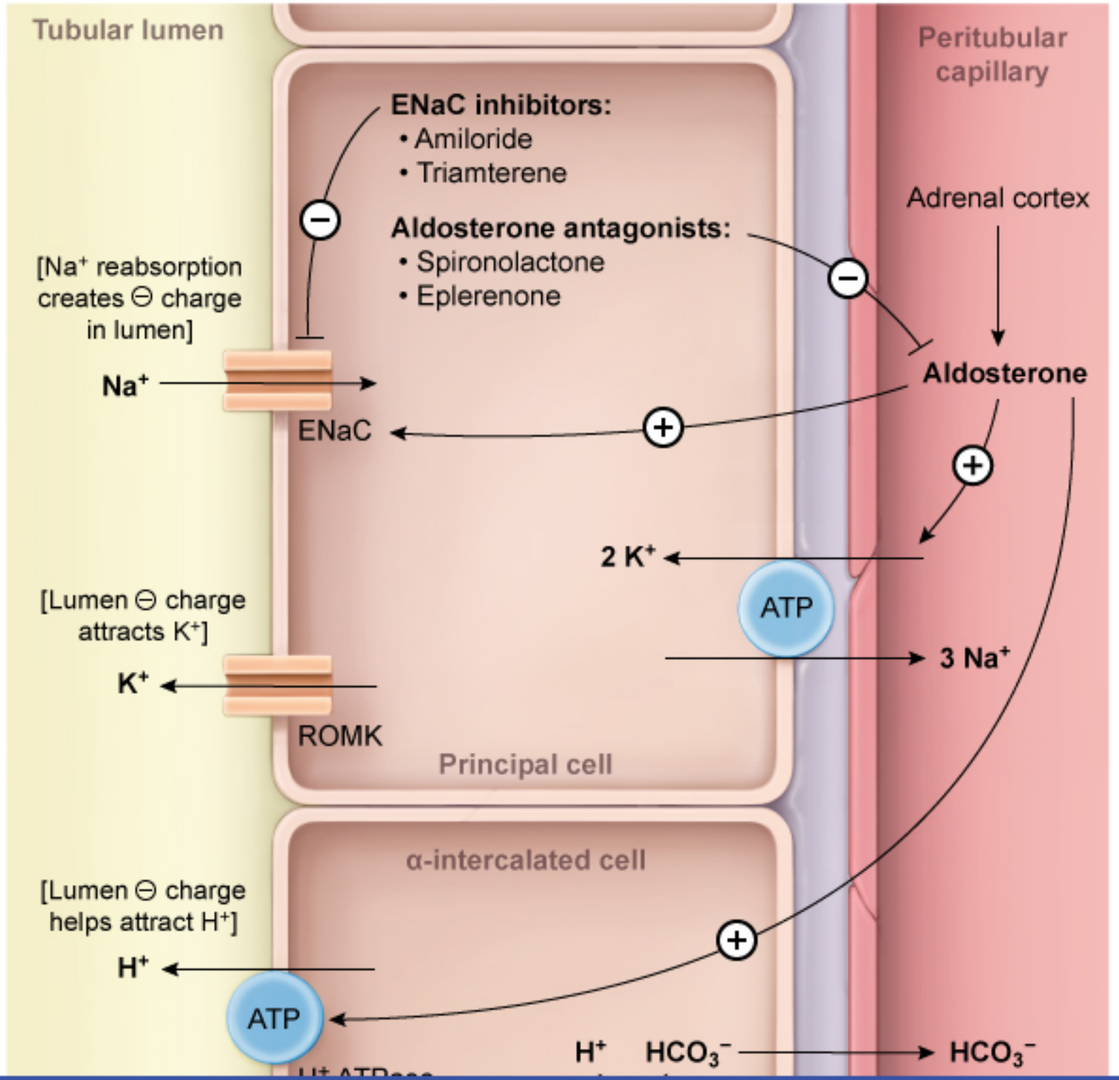
02 secs
Time Spent

05/27/2020
Last Updated

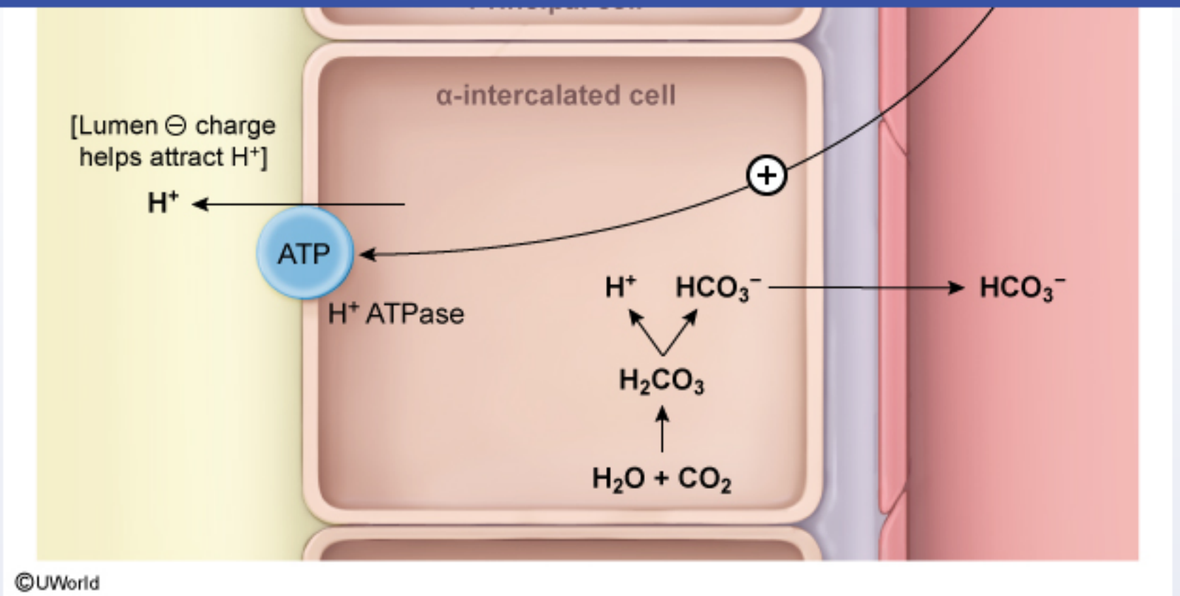
Explanation

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31

Action of aldosterone in the collecting duct of the nephron



1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31



This patient's fatigue and weight loss are likely due to **primary adrenal insufficiency** (Addison disease). Type 1 diabetes mellitus is caused by autoimmune destruction of pancreatic beta cells and is associated with an increased risk of other autoimmune endocrinopathies. Autoimmune adrenalitis is the most common cause of primary adrenal insufficiency and results from autoantibodies against all 3 zones of the adrenal cortex. Because the main defect is in the adrenal gland, **exogenous ACTH** administration **does not increase cortisol** levels. Decreased negative feedback of cortisol on the pituitary gland increases release of ACTH and melanocyte-stimulating hormone, resulting in **hyperpigmentation**. Patients with diabetes often have reduced insulin requirements due to decreased appetite, weight loss, and increased insulin sensitivity (glucocorticoids decrease insulin sensitivity).

Hypoaldosteronism in primary adrenal insufficiency leads to decreased Na^+ reabsorption and decreased urinary excretion of K^+ and H^+. Decreased H^+ excretion causes a nonanion gap metabolic acidosis with low plasma HCO_3^-. This leads to compensatory Cl^- retention to maintain electrical neutrality of the extracellular fluid. The hypotension induced by lack of aldosterone stimulates vasopressin release, increasing free water reabsorption and further exacerbating hyponatremia. As a result, patients with primary adrenal insufficiency present with **hyponatremia**, **hyperkalemia**, hyperchloremia, and **nonanion gap metabolic acidosis**.

(Choice A) Mineralocorticoid excess (ie, primary hyperaldosteronism) leads to Na^+ retention, urinary loss of K^+ and H^+, and metabolic alkalosis

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31

Hypoaldosteronism in primary adrenal insufficiency leads to decreased Na^+ reabsorption and decreased urinary excretion of K^+ and H^+. Decreased H^+ excretion causes a nonanion gap metabolic acidosis with low plasma HCO_3^-. This leads to compensatory Cl^- retention to maintain electrical neutrality of the extracellular fluid. The hypotension induced by lack of aldosterone stimulates vasopressin release, increasing free water reabsorption and further exacerbating hyponatremia. As a result, patients with primary adrenal insufficiency present with **hyponatremia**, **hyperkalemia**, hyperchloremia, and **nonanion gap metabolic acidosis**.

(Choice A) Mineralocorticoid excess (ie, primary hyperaldosteronism) leads to Na^+ retention, urinary loss of K^+ and H^+, and metabolic alkalosis (ie, increased plasma HCO_3^-). However, significant hypernatremia is avoided due to aldosterone escape.

(Choice C) Thiazide diuretics block Na^+/Cl^- reabsorption in the distal tubule. This allows more Na^+ to reach the collecting tubule, enhancing K^+ and H^+ excretion. Findings include hyponatremia, hypokalemia, and metabolic alkalosis.

(Choice D) Isolated hyperkalemia is usually due to excess dietary potassium intake or cell lysis (eg, hemolysis, rhabdomyolysis). Hyperkalemia can also be caused by decreased shift of K^+ into the cells due to insulin deficiency or occasionally by beta 2 antagonists (eg, metoprolol).

(Choice E) Normal serum sodium in the setting of hypokalemia and hyperchloremic metabolic acidosis suggests distal hypokalemic or proximal renal tubular acidosis.

Educational objective:
Patients with type 1 diabetes mellitus are at increased risk for other autoimmune endocrinopathies, including primary adrenal insufficiency (Addison disease). Electrolyte abnormalities in primary adrenal insufficiency include hyponatremia, hyperkalemia, hyperchloremia, and nonanion gap metabolic acidosis.

References

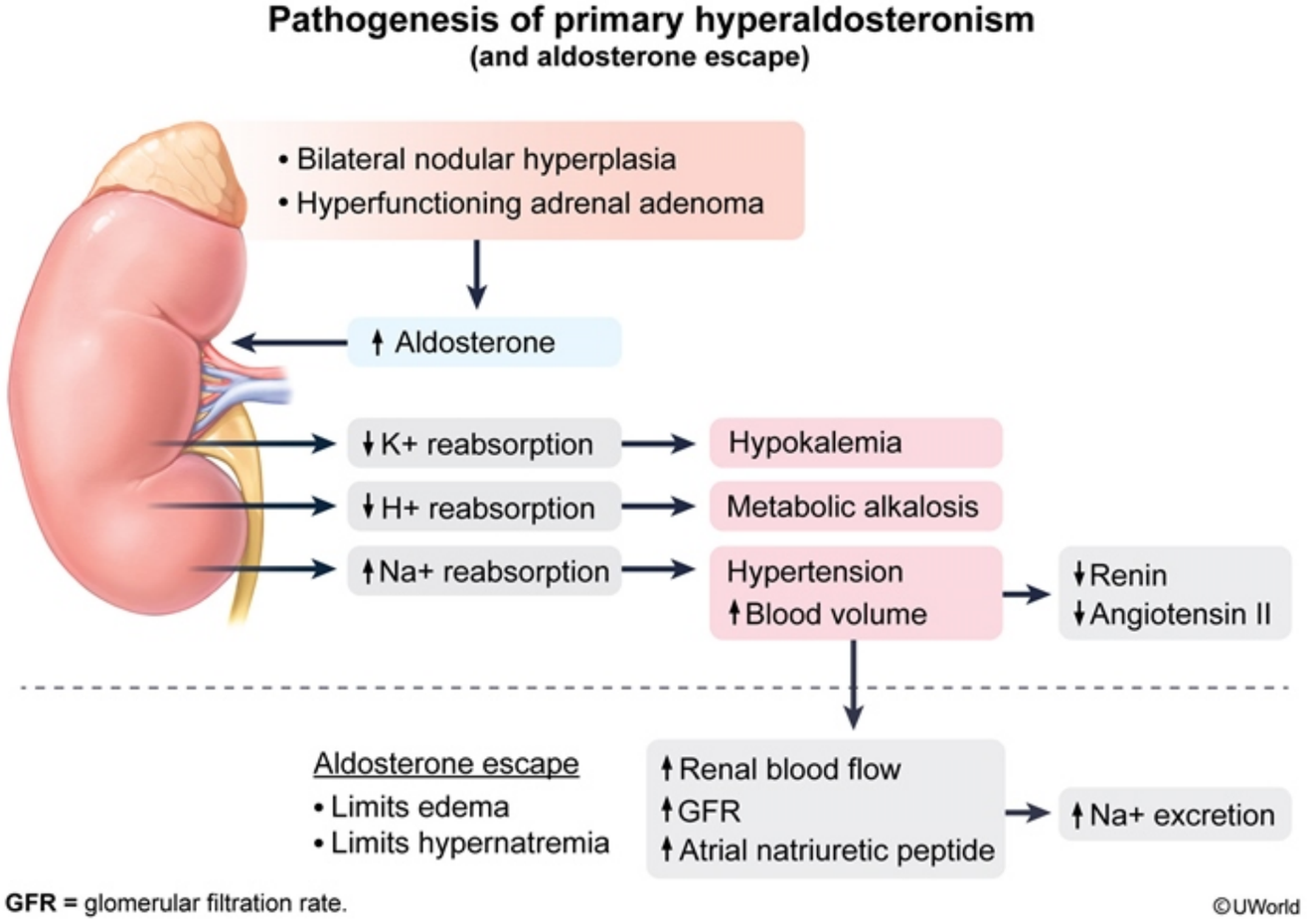
- Diagnosis and classification of Addison's disease (autoimmune adrenalitis).

Pathophysiology	Endocrine, Diabetes & Metabolism	Adrenal insufficiency
Subject	System	Topic

Copyright © UWorld. All rights reserved.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31

Exhibit Display



Zoom In | Zoom Out | Reset | Add To New Card | Existing Card

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31

A 50-year-old woman comes to the office to discuss weight gain. She has gained about 13.6 kg (30 lb) over the last 2 years, which she attributes to excessive eating and not exercising. The patient is otherwise feeling well, and her past medical history is unremarkable. However, she has a strong family history of type 2 diabetes mellitus. Blood pressure is 150/90 mm Hg and pulse is 75/min. BMI is 30.3 kg/m^2. Hyperpigmentation in skinfolds is noted at the neck as shown in the image below.

Laboratory testing shows a fasting blood glucose of 150 mg/dL and HbA1c of 8.0%. Elevated serum levels of which of the following substances are most likely contributing to this patient's disease process?

A. Beta-hydroxybutyrate

B. C-peptide

C. Free fatty acids

D. High-density lipoprotein

E. Low-density lipoprotein

Submit

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31

A 50-year-old woman comes to the office to discuss weight gain. She has gained about 13.6 kg (30 lb) over the last 2 years, which she attributes to excessive eating and not exercising. The patient is otherwise feeling well, and her past medical history is unremarkable. However, she has a strong family history of type 2 diabetes mellitus. Blood pressure is 150/90 mm Hg and pulse is 75/min. BMI is 30.3 kg/m^2. Hyperpigmentation in skinfolds is noted at the neck as shown in the image below.

Laboratory testing shows a fasting blood glucose of 150 mg/dL and HbA1c of 8.0%. Elevated serum levels of which of the following substances are most likely contributing to this patient's disease process?

A. Beta-hydroxybutyrate

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31

Laboratory testing shows a fasting blood glucose of 150 mg/dL and HbA1c of 8.0%. Elevated serum levels of which of the following substances are most likely contributing to this patient's disease process?

A. Beta-hydroxybutyrate

B. C-peptide

C. Free fatty acids

D. High-density lipoprotein

E. Low-density lipoprotein

Submit

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31

Laboratory testing shows a fasting blood glucose of 150 mg/dL and HbA1c of 8.0%. Elevated serum levels of which of the following substances are most likely contributing to this patient's disease process?

A. Beta-hydroxybutyrate (8%)

B. C-peptide (37%)

✓ C. Free fatty acids (29%)

D. High-density lipoprotein (0%)

E. Low-density lipoprotein (23%)

Omitted
Correct answer

29%
Answered correctly

07 secs
Time Spent

02/06/2020
Last Updated

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31

This patient has new-onset **type 2 diabetes mellitus** (T2DM), which results from a combination of **insulin resistance** and **relative insulin deficiency**. The early course of T2DM is characterized by increased insulin production and decreased sensitivity of target organs to the effects of insulin, although insulin levels may later decline as the disease progresses. In addition, this patient has acanthosis nigricans, which is another sign of insulin resistance.

Insulin resistance in adipose cells hinders the antilipolytic effects of insulin, leading to lipolysis and release of free fatty acids. In turn, chronically **elevated free fatty acid levels** contribute to insulin resistance by impairing insulin-dependent glucose uptake and increasing hepatic gluconeogenesis. Other factors that contribute to insulin resistance include obesity and a sedentary lifestyle.

This patient has new-onset **type 2 diabetes mellitus** (T2DM), which results from a combination of **insulin resistance** and **relative insulin deficiency**. The early course of T2DM is characterized by increased insulin production and decreased sensitivity of target organs to the effects of insulin, although insulin levels may later decline as the disease progresses. In addition, this patient has acanthosis nigricans, which is another sign of insulin resistance.

Insulin resistance in adipose cells hinders the antilipolytic effects of insulin, leading to lipolysis and release of free fatty acids. In turn, chronically **elevated free fatty acid levels** contribute to insulin resistance by impairing insulin-dependent glucose uptake and increasing hepatic gluconeogenesis. Other factors that contribute to insulin resistance include obesity and a sedentary lifestyle.

(Choice A) Absolute insulin deficiency in type 1 diabetes mellitus leads to increased gluconeogenesis and conversion of fatty acids to ketone bodies (eg, beta-hydroxybutyrate). Very high levels of ketone bodies are seen in diabetic ketoacidosis but are not typical in T2DM and do not interfere with the production or actions of insulin.

(Choice B) C-peptide is secreted with insulin in equimolar amounts from pancreatic beta cells. Patients with insulin resistance will have increased production of both insulin and C-peptide, but C-peptide does not cause insulin resistance.

(Choices D and E) The "metabolic syndrome" is a common collection of clinical features that includes elevated triglycerides, low HDL cholesterol, central obesity, hypertension, and elevated glucose. These patients typically have significant insulin resistance. However, elevated LDL and HDL levels do not contribute to insulin resistance or acanthosis nigricans.

Educational objective:
Type 2 diabetes mellitus is due to insulin resistance and relative insulin deficiency. Chronically elevated free fatty acid levels contribute to insulin resistance by impairing insulin-dependent glucose uptake and increasing hepatic gluconeogenesis.

References

- Free fatty acids and skeletal muscle insulin resistance.
- Obesity, insulin resistance and free fatty acids.
- Low-density-lipoprotein cholesterol concentrations and risk of incident diabetes: epidemiological and genetic insights from the Framingham Heart Study.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31

A 24-year-old man diagnosed with diabetes mellitus 2 years ago is brought to the emergency department after a temporary loss of consciousness. He was getting ready to eat and administered a preprandial insulin injection, but he was distracted by a phone call from work and ended up skipping the meal. His girlfriend found him passed out in his bedroom and administered glucagon immediately. The patient recovered consciousness within 15 minutes. Metabolic changes in which of the following organs are most likely responsible for this patient's recovery?

- A. Adipose tissue
- B. Adrenals
- C. Kidney
- D. Liver
- E. Pancreas
- F. Skeletal muscles
- G. Small intestine

Submit

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31

A 24-year-old man diagnosed with diabetes mellitus 2 years ago is brought to the emergency department after a temporary loss of consciousness. He was getting ready to eat and administered a preprandial insulin injection, but he was distracted by a phone call from work and ended up skipping the meal. His girlfriend found him passed out in his bedroom and administered glucagon immediately. The patient recovered consciousness within 15 minutes. Metabolic changes in which of the following organs are most likely responsible for this patient's recovery?

- A. Adipose tissue (2%)
- B. Adrenals (1%)
- C. Kidney (0%)
- ✓ D. Liver (86%)
- E. Pancreas (3%)
- F. Skeletal muscles (4%)
- G. Small intestine (0%)

Omitted
Correct answer
D

86%
Answered correctly

01 sec
Time Spent

03/22/2020
Last Updated

Explanation

Glucagon increases serum glucose by increasing hepatic glucose production via **glycogenolysis** (breakdown of glycogen) and **gluconeogenesis** (production of glucose from noncarbohydrate sources). Glucagon-induced glycogenolysis is the predominant initial means of rapidly increasing blood glucose levels during hypoglycemia.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31

Glucagon increases serum glucose by increasing hepatic glucose production via **glycogenolysis** (breakdown of glycogen) and **gluconeogenesis** (production of glucose from noncarbohydrate sources). Glucagon-induced glycogenolysis is the predominant initial means of rapidly increasing blood glucose levels during hypoglycemia.

Glucagon functions by stimulating G protein–coupled receptors on hepatocytes, increasing intracellular cAMP concentration and activating protein kinase A. This leads to activation of the key glycogenolytic enzyme, glycogen phosphorylase. It also stimulates gluconeogenesis by activating rate-limiting gluconeogenetic enzymes (eg, pyruvate carboxylase, phosphoenolpyruvate carboxykinase) and decreasing intracellular fructose-2,6-bisphosphate levels (inhibiting glycolysis).

(Choices A, B, and F) Epinephrine from the adrenals increases glucose by multiple mechanisms, including increased glycogenolysis and gluconeogenesis in the liver and decreased glucose uptake by skeletal muscle. Epinephrine also causes increased alanine release from skeletal muscle, which serves as a source of gluconeogenesis in the liver. In adipose tissue, epinephrine increases the breakdown of triglycerides, thereby increasing circulating free fatty acids and glycerol that can be utilized as gluconeogenetic substrates.

(Choice C) During the first 12 hours of fasting, hepatic glycogenolysis is the source for most of the body's glucose. When hypoglycemia is sustained, gluconeogenesis in the renal cortex becomes an important glucose source. Epinephrine is more effective than glucagon in stimulating renal gluconeogenesis.

(Choice E) Glucagon and insulin are pancreatic hormones that act as key blood glucose regulators. Insulin decreases blood glucose levels and suppresses glucagon secretion. Although it sounds counterintuitive, glucagon stimulates insulin secretion by acting on the pancreatic beta cells (allowing glucose to be taken up by insulin-sensitive tissues).

(Choice G) The treatment of choice in hypoglycemic patients without an altered sensorium is to administer glucose orally as glucose is a monosaccharide that gets absorbed rapidly from the gastrointestinal tract.

Educational objective:
Glucagon increases serum glucose by increasing hepatic glycogenolysis and gluconeogenesis. Glucagon also stimulates insulin secretion from the pancreas. Unlike epinephrine, glucagon has an insignificant effect on glucose homeostasis in the skeletal muscle, adipose tissue, and renal cortex.

References

- Physiologic action of glucagon on liver glucose metabolism.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31

rate-limiting gluconeogenetic enzymes (eg, pyruvate carboxylase, phosphoenolpyruvate carboxykinase) and decreasing intracellular fructose-2,6-bisphosphate levels (inhibiting glycolysis).

(Choices A, B, and F) Epinephrine from the adrenals increases glucose by multiple mechanisms, including increased glycogenolysis and gluconeogenesis in the liver and decreased glucose uptake by skeletal muscle. Epinephrine also causes increased alanine release from skeletal muscle, which serves as a source of gluconeogenesis in the liver. In adipose tissue, epinephrine increases the breakdown of triglycerides, thereby increasing circulating free fatty acids and glycerol that can be utilized as gluconeogenetic substrates.

(Choice C) During the first 12 hours of fasting, hepatic glycogenolysis is the source for most of the body's glucose. When hypoglycemia is sustained, gluconeogenesis in the renal cortex becomes an important glucose source. Epinephrine is more effective than glucagon in stimulating renal gluconeogenesis.

(Choice E) Glucagon and insulin are pancreatic hormones that act as key blood glucose regulators. Insulin decreases blood glucose levels and suppresses glucagon secretion. Although it sounds counterintuitive, glucagon stimulates insulin secretion by acting on the pancreatic beta cells (allowing glucose to be taken up by insulin-sensitive tissues).

(Choice G) The treatment of choice in hypoglycemic patients without an altered sensorium is to administer glucose orally as glucose is a monosaccharide that gets absorbed rapidly from the gastrointestinal tract.

Educational objective:
Glucagon increases serum glucose by increasing hepatic glycogenolysis and gluconeogenesis. Glucagon also stimulates insulin secretion from the pancreas. Unlike epinephrine, glucagon has an insignificant effect on glucose homeostasis in the skeletal muscle, adipose tissue, and renal cortex.

References

- Physiologic action of glucagon on liver glucose metabolism.

Pathophysiology	Endocrine, Diabetes & Metabolism	Hypoglycemia
Subject	System	Topic

Copyright © UWorld. All rights reserved.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31

A 40-year-old woman is evaluated for intermittent headaches, insomnia, diaphoresis, and unintentional weight loss over the past several months. The patient has no other medical problems and takes no medications. She does not use tobacco, alcohol, or illicit drugs and has no significant family history. The patient is found to have a neoplastic mass producing excessive amounts of hormones that are causing her symptoms. Surgical resection of the abnormal tissue is performed with no operative complications. Microscopic examination of the tumor cells shows electron-dense, membrane-bound secretory granules. Immunohistochemistry is positive for synaptophysin, chromogranin, and neuron-specific enolase. The abnormal tissue most likely originated from which of the following?

A. Adrenal cortex

B. Adrenal medulla

C. Ovary

D. Parathyroid gland

E. Thyroid follicles

Submit

A 40-year-old woman is evaluated for intermittent headaches, insomnia, diaphoresis, and unintentional weight loss over the past several months. The patient has no other medical problems and takes no medications. She does not use tobacco, alcohol, or illicit drugs and has no significant family history. The patient is found to have a neoplastic mass producing excessive amounts of hormones that are causing her symptoms. Surgical resection of the abnormal tissue is performed with no operative complications. Microscopic examination of the tumor cells shows electron-dense, membrane-bound secretory granules. Immunohistochemistry is positive for synaptophysin, chromogranin, and neuron-specific enolase. The abnormal tissue most likely originated from which of the following?

- A. Adrenal cortex (3%)
- ✓ B. Adrenal medulla (85%)
- C. Ovary (1%)
- D. Parathyroid gland (1%)
- E. Thyroid follicles (8%)

Omitted
Correct answer
B

85%
Answered correctly

01 sec
Time Spent

05/23/2020
Last Updated

Explanation

Pheochromocytoma	
	• Arises from neuroendocrine cells in **adrenal medulla** • 25% inherited:

Pheochromocytoma	

Pathogenesis	• Arises from neuroendocrine cells in **adrenal medulla**
	• 25% inherited:
	  ◦ *VHL* gene (von Hippel-Lindau)
	  ◦ *RET* gene (multiple endocrine neoplasia type 2)
	  ◦ *NF1* gene (neurofibromatosis)
	• Symptoms result from **increased catecholamine secretion**

Symptoms	• Headache • Tachycardia/palpitations • Sweating • Hypertension
Rule of 10s	• 10% bilateral • 10% extraadrenal (paragangliomas) • 10% malignant
Diagnosis	Elevated urinary & plasma catecholamines & metanephrines

Pheochromocytoma is a tumor of the **chromaffin cells** of the **adrenal medulla** characterized by excess production of **catecholamines** (norepinephrine, epinephrine, dopamine). Fluctuating catecholamine release results in increased vascular tone and hypertension, often associated with episodic headache, diaphoresis, and palpitations. The diagnosis is confirmed by detecting elevated levels of urinary and plasma catecholamines and metanephrines (catecholamine breakdown products).

Histopathology shows a highly vascular tumor with nests of spindle-shaped or polygonal cells. The neurohormonal character of the cells is confirmed with stains for **synaptophysin**, **chromogranin**, and **neuron-specific enolase**, and electron microscopy may show dense membrane-bound granules containing catecholamines.

(Choices A and C) Syndromes associated with steroid hormone-producing tumors of the adrenal cortex include hypercortisolism (Cushing

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31

Pheochromocytoma is a tumor of the **chromaffin cells** of the **adrenal medulla** characterized by excess production of **catecholamines** (norepinephrine, epinephrine, dopamine). Fluctuating catecholamine release results in increased vascular tone and hypertension, often associated with episodic headache, diaphoresis, and palpitations. The diagnosis is confirmed by detecting elevated levels of urinary and plasma catecholamines and metanephrines (catecholamine breakdown products).

Histopathology shows a highly vascular tumor with nests of spindle-shaped or polygonal cells. The neurohormonal character of the cells is confirmed with stains for **synaptophysin**, **chromogranin**, and **neuron-specific enolase**, and electron microscopy may show dense membrane-bound granules containing catecholamines.

(Choices A and C) Syndromes associated with steroid hormone-producing tumors of the adrenal cortex include hypercortisolism (Cushing syndrome), hyperaldosteronism (hypertension, hypokalemia, metabolic alkalosis), and hyperandrogenism (hirsutism, acne, androgenetic hair loss). Metabolically active ovarian tumors also can cause hyperandrogenism. Overproduction of steroid hormones is apparent on electron microscopy as well-developed smooth endoplasmic reticulum rather than membrane-bound secretory granules.

(Choice D) Parathyroid adenomas (or carcinomas) cause primary hyperparathyroidism resulting in hypercalcemia. Characteristic symptoms include constipation, abdominal pain, bone pain, and neuropsychiatric symptoms.

(Choice E) Toxic nodular thyroid disease could produce this patient's symptoms (eg, diaphoresis, weight loss). However, metabolically active thyroid adenomas typically show a follicular structure, with uniform cells and large amounts of follicular colloid.

Educational objective:
Pheochromocytoma is a tumor arising from the chromaffin cells of the adrenal medulla characterized by excess production of catecholamines. Clinical features include episodic hypertension, diaphoresis, and palpitations. Microscopic examination of the tumor cells shows electron-dense, membrane-bound secretory granules, and immunohistochemistry is positive for synaptophysin, chromogranin, and neuron-specific enolase.

References

- Pheochromocytoma and paraganglioma: an Endocrine Society clinical practice guideline.

Pathophysiology	Endocrine, Diabetes & Metabolism	Pheochromocytoma
Subject	System	Topic

Copyright © UWorld. All rights reserved.

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31

A 27-year-old man is brought to the emergency department due to confusion. His roommate says that he has been binge drinking for the last 5 days and probably has had very little to eat. The patient's medical history is significant for alcohol-related seizures 1 year ago. He had been sober until 2 weeks ago, when he started drinking again. The patient's past medical history is otherwise unremarkable. On examination, he responds to voice but does not follow commands. Fingerstick glucose is 35 mg/dL and urine is strongly positive for ketones. Suppression of which of the following is the primary cause of this patient's hypoglycemia?

A. Gluconeogenesis
B. Glycogenolysis
C. Insulin clearance
D. Insulin sensitivity
E. Lipolysis

Submit

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31

A 27-year-old man is brought to the emergency department due to confusion. His roommate says that he has been binge drinking for the last 5 days and probably has had very little to eat. The patient's medical history is significant for alcohol-related seizures 1 year ago. He had been sober until 2 weeks ago, when he started drinking again. The patient's past medical history is otherwise unremarkable. On examination, he responds to voice but does not follow commands. Fingerstick glucose is 35 mg/dL and urine is strongly positive for ketones. Suppression of which of the following is the primary cause of this patient's hypoglycemia?

- ✓ A. Gluconeogenesis (73%)
- B. Glycogenolysis (13%)
- C. Insulin clearance (2%)
- D. Insulin sensitivity (4%)
- E. Lipolysis (6%)

Omitted
Correct answer
A

73%
Answered correctly

01 sec
Time Spent

06/01/2020
Last Updated

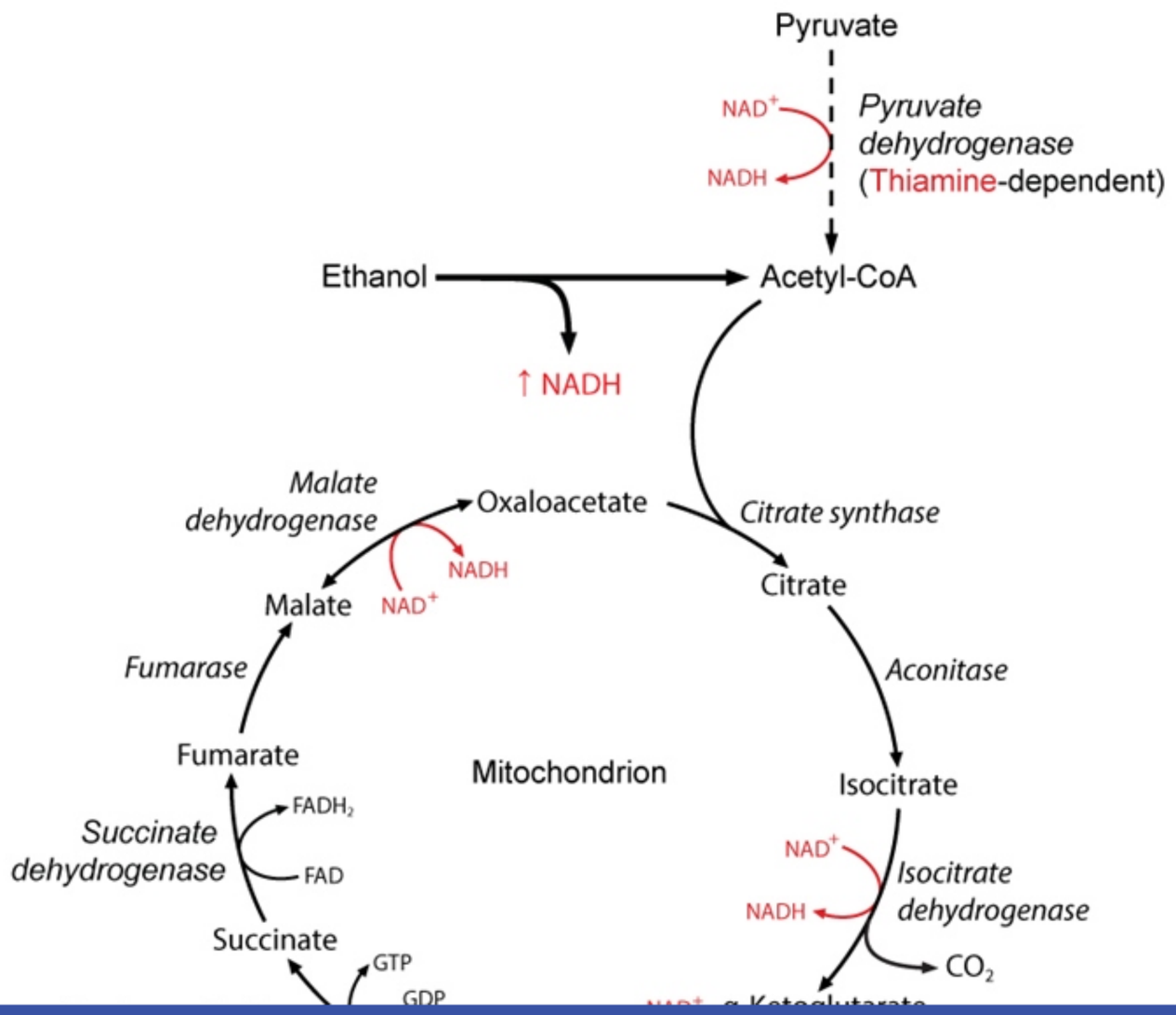
Explanation

Inhibition of the citric acid cycle by ethanol

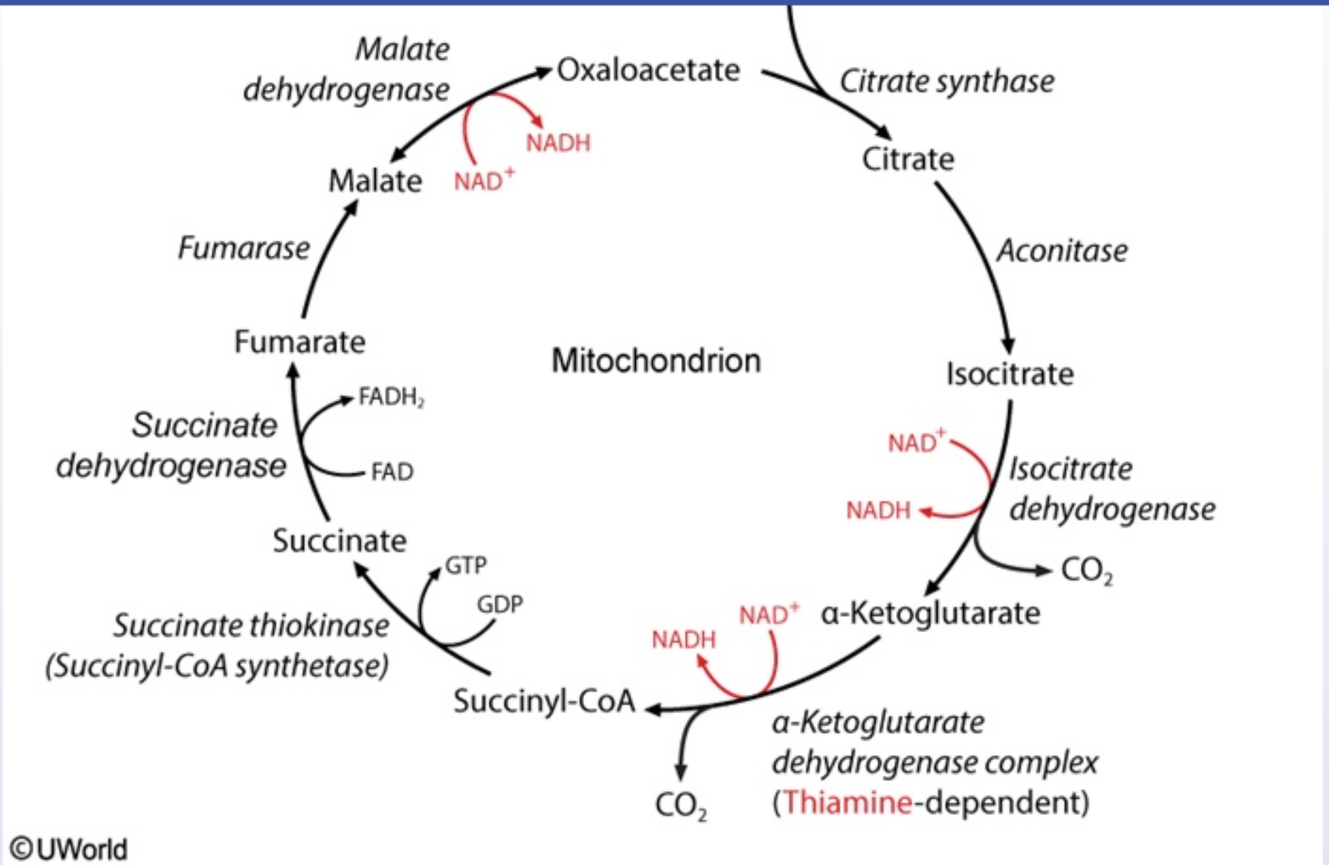
Pyruvate

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31

Inhibition of the citric acid cycle by ethanol

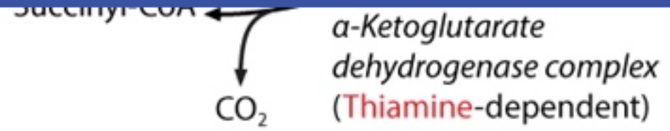


1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31



The metabolism of **ethanol** by alcohol dehydrogenase and aldehyde dehydrogenase reduces NAD^+ to NADH and increases the **NADH/NAD^+ ratio**. This inhibits all other pathways requiring NAD^+, including reactions required for gluconeogenesis. In particular, lactate cannot be converted to pyruvate, and instead the reaction is driven from pyruvate toward lactate. In addition, excess NADH inhibits the conversion of malate to oxaloacetate. Pyruvate and oxaloacetate are intermediates in gluconeogenesis; therefore, conversion of these molecules to lactate and malate **inhibits gluconeogenesis**.

Alcohol does not inhibit glycogenolysis **(Choice B)**, and so in the initial phase of binge drinking (heavy alcohol intake with reduced nutritional carbohydrate intake), hepatic glycogenolysis is able to maintain euglycemia. However, after a prolonged binge, hepatic glycogen is eventually



©UWorld

The metabolism of **ethanol** by alcohol dehydrogenase and aldehyde dehydrogenase reduces NAD^+ to NADH and increases the **NADH/NAD^+ ratio**. This inhibits all other pathways requiring NAD^+, including reactions required for gluconeogenesis. In particular, lactate cannot be converted to pyruvate, and instead the reaction is driven from pyruvate toward lactate. In addition, excess NADH inhibits the conversion of malate to oxaloacetate. Pyruvate and oxaloacetate are intermediates in gluconeogenesis; therefore, conversion of these molecules to lactate and malate **inhibits gluconeogenesis**.

Alcohol does not inhibit glycogenolysis **(Choice B)**, and so in the initial phase of binge drinking (heavy alcohol intake with reduced nutritional carbohydrate intake), hepatic glycogenolysis is able to maintain euglycemia. However, after a prolonged binge, hepatic glycogen is eventually depleted and blood glucose levels drop.

(Choices C and D) Ethanol has no direct effect on insulin sensitivity. Impaired clearance of insulin is a major contributor to hypoglycemia in patients with advanced renal insufficiency.

(Choice E) Excess NADH inhibits free fatty acid oxidation, thereby diverting free fatty acids away from lipolysis to the formation of triglycerides. This contributes to hepatic steatosis in alcoholic patients but does not cause hypoglycemia.

Educational objective:
Ethanol inhibits gluconeogenesis and can cause hypoglycemia once hepatic glycogen stores are depleted.

References

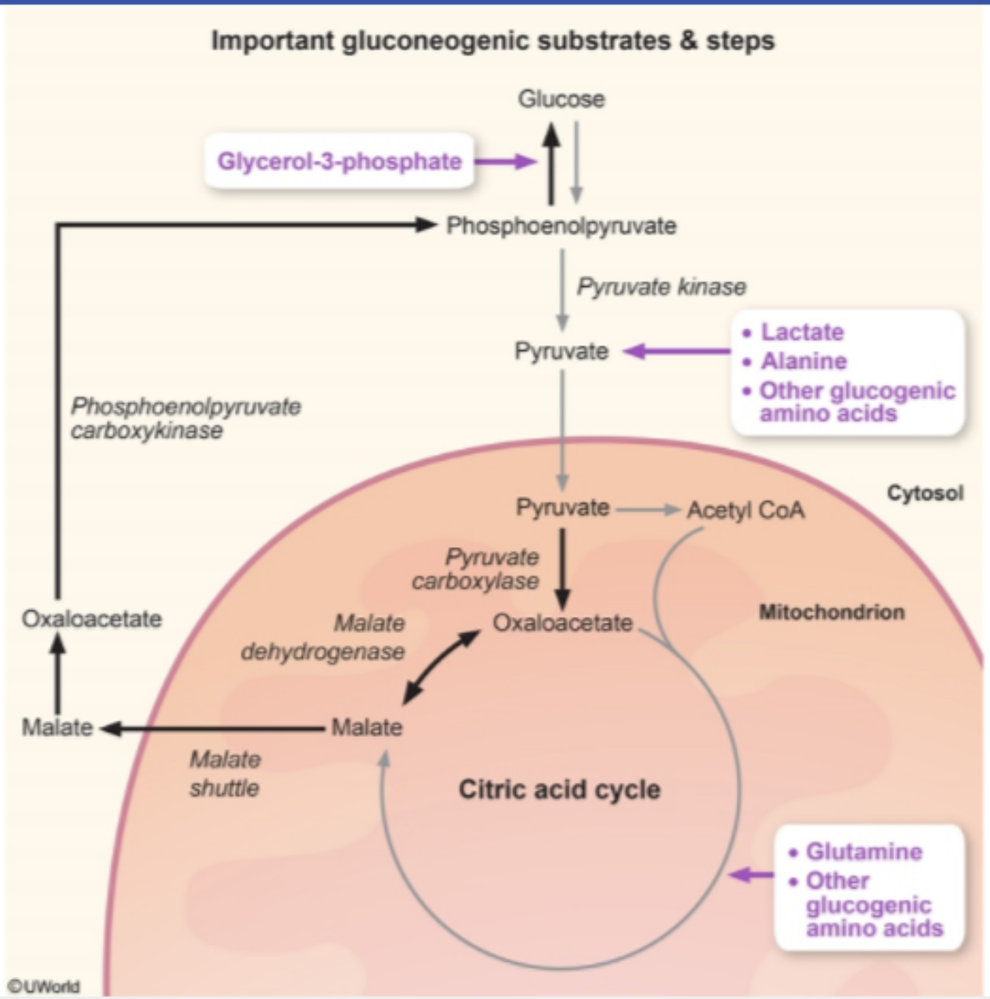
- Case of alcoholic ketoacidosis accompanied with severe hypoglycemia.

Pathophysiology	Endocrine, Diabetes & Metabolism	Gluconeogenesis
Subject	System	Topic

Copyright © UWorld. All rights reserved.

Succinyl-CoA ← α-Ketoglutarate

Exhibit Display



Zoom In | Zoom Out | Reset | Add To New Card | Existing Card

A 45-year-old woman calls 911 due to severe chest pain and dyspnea. The emergency medical team finds the patient unresponsive with no pulse, and she does not revive despite extensive cardiopulmonary resuscitation efforts. She had a prolonged history of systemic lupus erythematosus treated with multiple medications and was recently evaluated for progressive muscle weakness. Records from the patient's most recent office visit show an elevated blood pressure and examination findings of facial plethora, truncal obesity, and skin ecchymoses. She was also found to have mild hyperglycemia. Medical history included a left hip replacement for osteonecrosis of the femoral head 1 year ago. At autopsy, she is found to have an occluding thrombus in the left main coronary artery, which likely led to sudden cardiac death. Examination of this patient's adrenal glands is most likely to reveal which of the following findings?

A. Adrenocortical adenoma
B. Bilateral cortical atrophy
C. Diffuse cortical hyperplasia
D. Diffuse cortical hypertrophy
E. Nodular cortical hyperplasia

Submit

A 45-year-old woman calls 911 due to severe chest pain and dyspnea. The emergency medical team finds the patient unresponsive with no pulse, and she does not revive despite extensive cardiopulmonary resuscitation efforts. She had a prolonged history of systemic lupus erythematosus treated with multiple medications and was recently evaluated for progressive muscle weakness. Records from the patient's most recent office visit show an elevated blood pressure and examination findings of facial plethora, truncal obesity, and skin ecchymoses. She was also found to have mild hyperglycemia. Medical history included a left hip replacement for osteonecrosis of the femoral head 1 year ago. At autopsy, she is found to have an occluding thrombus in the left main coronary artery, which likely led to sudden cardiac death. Examination of this patient's adrenal glands is most likely to reveal which of the following findings?

A. Adrenocortical adenoma (8%)
✓ B. Bilateral cortical atrophy (66%)
C. Diffuse cortical hyperplasia (15%)
D. Diffuse cortical hypertrophy (7%)
E. Nodular cortical hyperplasia (1%)

Omitted
Correct answer
B

66%
Answered correctly

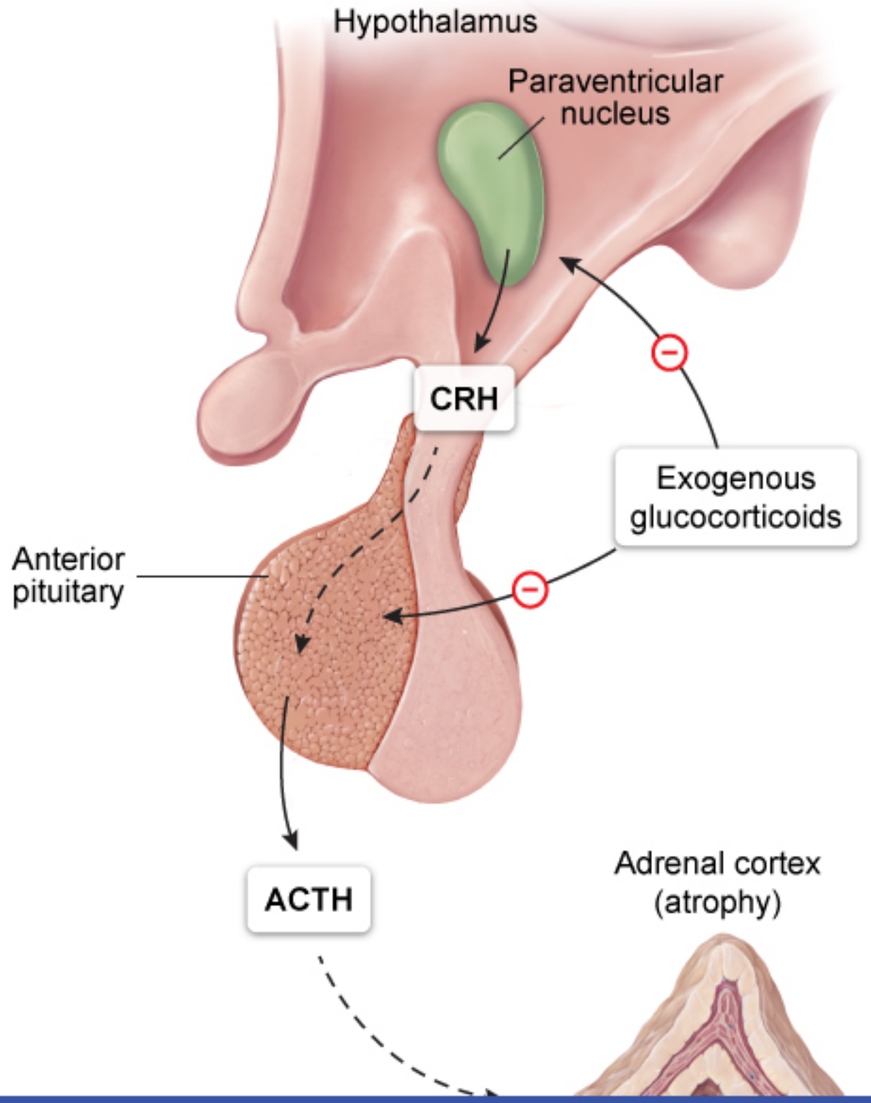
03 secs
Time Spent

05/17/2020
Last Updated

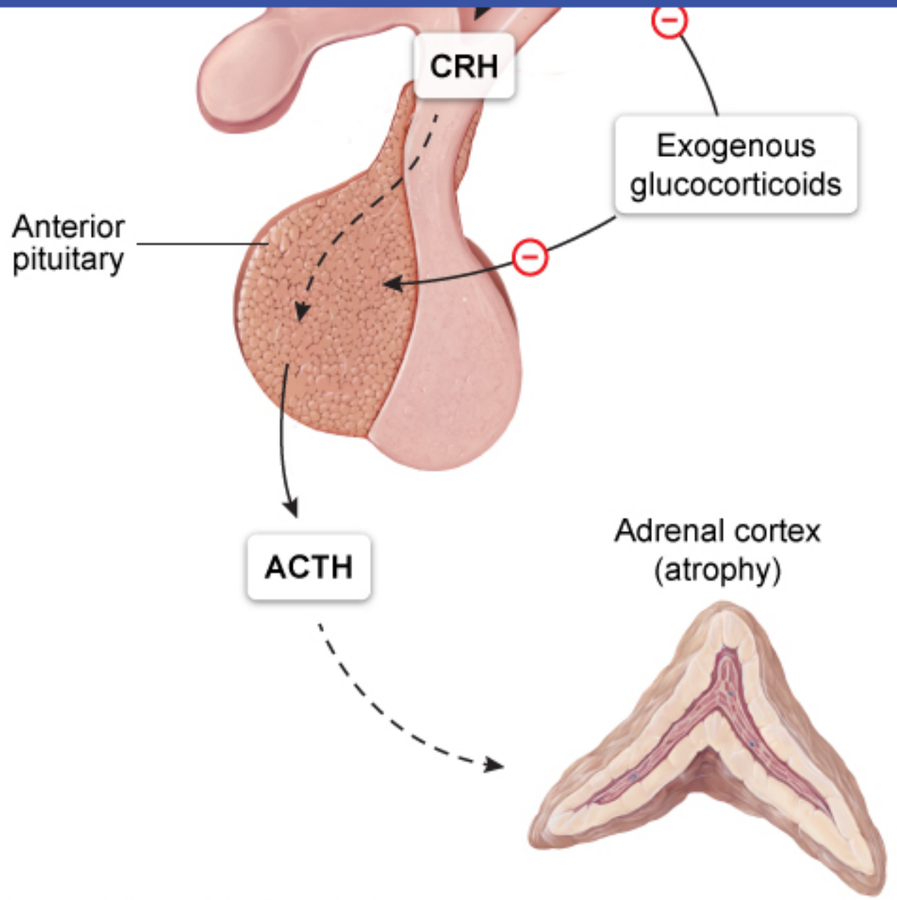
Explanation

10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40

Suppression of hypothalamic-pituitary-adrenal axis



10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40



CRH = corticotropin-releasing hormone.

©UWorld

This patient has features of hypercortisolism, including hypertension, central obesity, muscular weakness, ecchymoses, and hyperglycemia. She most likely developed **iatrogenic Cushing syndrome** due to prolonged administration of glucocorticoids for management of systemic lupus erythematosus (SLE). **Chronic glucocorticoid use** can also cause osteonecrosis, and both Cushing syndrome and SLE itself can increase the risk for atherosclerosis and acute coronary events (as in this patient).

Exogenous glucocorticoid use **inhibits the entire hypothalamic-pituitary-adrenal axis**, leading to low levels of corticotropin-releasing hormone

CRH = corticotropin-releasing hormone.
©UWorld

This patient has features of hypercortisolism, including hypertension, central obesity, muscular weakness, ecchymoses, and hyperglycemia. She most likely developed **iatrogenic Cushing syndrome** due to prolonged administration of glucocorticoids for management of systemic lupus erythematosus (SLE). **Chronic glucocorticoid use** can also cause osteonecrosis, and both Cushing syndrome and SLE itself can increase the risk for atherosclerosis and acute coronary events (as in this patient).

Exogenous glucocorticoid use **inhibits the entire hypothalamic-pituitary-adrenal axis**, leading to low levels of corticotropin-releasing hormone (CRH), ACTH, and endogenous cortisol. ACTH exerts a potent trophic (ie, growth promoting) effect on the adrenal zona fasciculata and reticularis; **long-term** suppression leads to **adrenocortical atrophy** (the zona glomerulosa is spared as angiotensin II is its primary trophic hormone). **Sudden cessation** of glucocorticoids after prolonged use can precipitate adrenocortical insufficiency and **adrenal crisis**.

(Choice A) Endogenous Cushing syndrome can be caused by an autonomous cortisol-producing adrenal tumor. However, this patient's history is more suggestive of exogenous glucocorticoid use.

(Choices C, D, and E) Bilateral cortical hyperplasia and hypertrophy occurs in patients with ACTH excess (eg, pituitary corticotroph adenoma [Cushing disease]). Varying degrees of adrenocortical nodularity can also be seen. However, this patient was likely taking exogenous glucocorticoids, which would suppress ACTH release and lead to adrenocortical atrophy.

Educational objective:
Long-term use of supraphysiologic doses of glucocorticoids causes suppression of the hypothalamic-pituitary-adrenal axis, which in turn leads to bilateral adrenocortical atrophy involving the zona fasciculata and reticularis. Sudden cessation of the exogenous corticosteroids can precipitate adrenal crisis.

References

- Management issues with exogenous steroid therapy.

Pathophysiology	Endocrine, Diabetes & Metabolism	Cushing syndrome
Subject	System	Topic

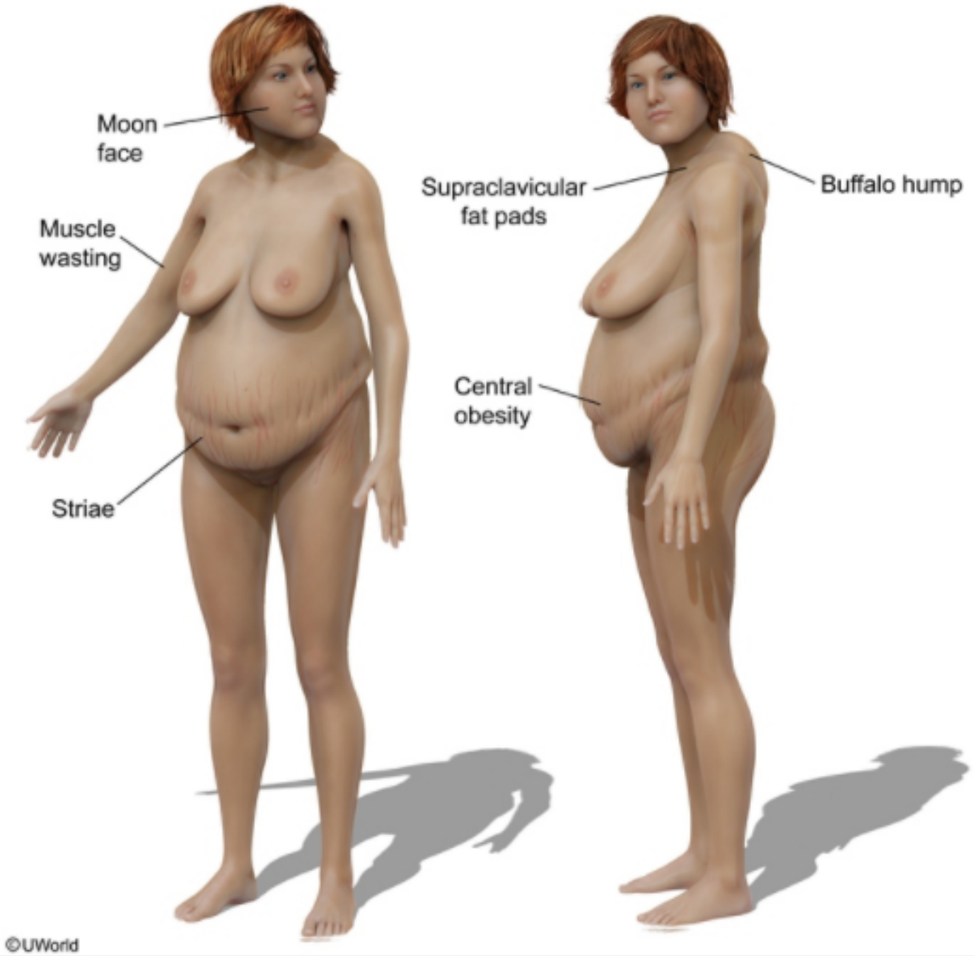
Copyright © UWorld. All rights reserved.

CRH = corticotropin-releasing hormone.

©UWorld

Exhibit Display

Features of Cushing syndrome



©UWorld

Zoom In | Zoom Out | Reset | Add To New Card | Existing Card

10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40

A 32-year-old man comes to the office due to vision problems. Over the last 6 weeks, he has had several "near-misses" while driving, having been nearly hit by cars coming from both the right and left sides. He also reports frequent headaches. The patient has no prior medical conditions and takes no medications. He does not use tobacco, alcohol, or illicit drugs. Physical examination reveals deficits in the bilateral temporal visual fields. Extraocular movements are bilaterally intact, and the remainder of the neurological examination shows no abnormalities. Which of the following additional findings is most likely to be present in this patient?

A. Decreased libido
B. Enlarged jaw bone
C. Excessive urination
D. Heat intolerance
E. Skin hyperpigmentation
F. Skin thinning

Submit

A 32-year-old man comes to the office due to vision problems. Over the last 6 weeks, he has had several "near-misses" while driving, having been nearly hit by cars coming from both the right and left sides. He also reports frequent headaches. The patient has no prior medical conditions and takes no medications. He does not use tobacco, alcohol, or illicit drugs. Physical examination reveals deficits in the bilateral temporal visual fields. Extraocular movements are bilaterally intact, and the remainder of the neurological examination shows no abnormalities. Which of the following additional findings is most likely to be present in this patient?

- ✓ A. Decreased libido (81%)
- B. Enlarged jaw bone (5%)
- C. Excessive urination (3%)
- D. Heat intolerance (2%)
- E. Skin hyperpigmentation (4%)
- F. Skin thinning (1%)

Omitted
Correct answer
A

81%
Answered correctly

02 secs
Time Spent

02/16/2020
Last Updated

Explanation

Pituitary adenomas	
Cell type	Clinical features of tumor

Pituitary adenomas	
Cell type	**Clinical features of tumor**
Lactotroph (prolactin)	• Hypogonadism, infertility (men) • Galactorrhea, amenorrhea (women)
Corticotroph (ACTH)	• Cushing disease
Somatotroph (growth hormone)	• Acromegaly (adults) • Gigantism (children)
Thyrotroph (TSH)	• Thyrotoxicosis
Gonadotroph (LH, FSH)	• Nonfunctioning (hypopituitarism) • Mass effect

This patient's symptoms are worrisome for a **pituitary tumor**. Large tumors can cause **headaches** due to mass effect, and compression of the optic chiasm by suprasellar extension of the tumor can cause **bitemporal hemianopsia**. These tumors can also cause loss of normal pituitary function by compression of surrounding cells. Pituitary adenomas typically arise from 1 of the 5 major cell types of the anterior pituitary; physiologic symptoms depend on the hormones produced by the tumor. The most common hormonally active (functional) adenomas are prolactin-secreting adenomas (**prolactinomas**).

Prolactin is a peptide hormone whose primary action is maintenance of lactation in the postpartum period; prolactinomas classically cause galactorrhea in premenopausal women. Prolactin also suppresses GnRH production from the hypothalamus, which in women leads to amenorrhea and in men causes **hypogonadism** (eg, impotence, **decreased libido**, infertility). Because the symptoms of hyperprolactinemia in men and postmenopausal women are often mild and nonspecific, patients may not seek care until the tumors are large and cause mass effect symptoms.

This patient's symptoms are worrisome for a **pituitary tumor**. Large tumors can cause **headaches** due to mass effect, and compression of the optic chiasm by suprasellar extension of the tumor can cause **bitemporal hemianopsia**. These tumors can also cause loss of normal pituitary function by compression of surrounding cells. Pituitary adenomas typically arise from 1 of the 5 major cell types of the anterior pituitary; physiologic symptoms depend on the hormones produced by the tumor. The most common hormonally active (functional) adenomas are prolactin-secreting adenomas (**prolactinomas**).

Prolactin is a peptide hormone whose primary action is maintenance of lactation in the postpartum period; prolactinomas classically cause galactorrhea in premenopausal women. Prolactin also suppresses GnRH production from the hypothalamus, which in women leads to amenorrhea and in men causes **hypogonadism** (eg, impotence, **decreased libido**, infertility). Because the symptoms of hyperprolactinemia in men and postmenopausal women are often mild and nonspecific, patients may not seek care until the tumors are large and cause mass effect symptoms.

(Choices B, D, and F) Somatotroph (growth hormone-secreting) adenomas can present with gigantism (in children) or acromegaly in adults. Thyrotroph (TSH-secreting) adenomas cause central hyperthyroidism (eg, heat intolerance, tachycardia). Thinning of the skin, typically manifesting as abdominal stria, is a characteristic feature of Cushing syndrome; when hypercortisolism is due to a corticotroph (ACTH-producing) adenoma, it is referred to as Cushing disease. These tumors are significantly less common than prolactinomas.

(Choice C) Mass lesions involving the pituitary stalk or posterior pituitary could cause headaches and bitemporal hemianopsia in addition to central diabetes insipidus (due to decreased release of antidiuretic hormone [ADH] from the posterior pituitary). However, polyuria is typically only transient (lasting <6 weeks) because the hypothalamus is able to bypass the pituitary and directly release ADH into the circulation.

(Choice E) Hyperpigmentation in the context of pituitary disease is typically due to hypersecretion of ACTH, either due to a corticotroph adenoma or in response to primary adrenal insufficiency.

Educational objective:
Pituitary tumors can present with headaches, bitemporal hemianopsia, and hypopituitarism; the most common hormonally active (functional) adenomas are prolactin-secreting adenomas (prolactinomas). Prolactinomas can cause galactorrhea and amenorrhea in women. In men, they often present with hypogonadism.

References

- Progress in the diagnosis and classification of pituitary adenomas.

Prolactin is a peptide hormone whose primary action is maintenance of lactation in the postpartum period; prolactinomas classically cause galactorrhea in premenopausal women. Prolactin also suppresses GnRH production from the hypothalamus, which in women leads to amenorrhea and in men causes **hypogonadism** (eg, impotence, **decreased libido**, infertility). Because the symptoms of hyperprolactinemia in men and postmenopausal women are often mild and nonspecific, patients may not seek care until the tumors are large and cause mass effect symptoms.

(Choices B, D, and F) Somatotroph (growth hormone-secreting) adenomas can present with gigantism (in children) or acromegaly in adults. Thyrotroph (TSH-secreting) adenomas cause central hyperthyroidism (eg, heat intolerance, tachycardia). Thinning of the skin, typically manifesting as abdominal stria, is a characteristic feature of Cushing syndrome; when hypercortisolism is due to a corticotroph (ACTH-producing) adenoma, it is referred to as Cushing disease. These tumors are significantly less common than prolactinomas.

(Choice C) Mass lesions involving the pituitary stalk or posterior pituitary could cause headaches and bitemporal hemianopsia in addition to central diabetes insipidus (due to decreased release of antidiuretic hormone [ADH] from the posterior pituitary). However, polyuria is typically only transient (lasting <6 weeks) because the hypothalamus is able to bypass the pituitary and directly release ADH into the circulation.

(Choice E) Hyperpigmentation in the context of pituitary disease is typically due to hypersecretion of ACTH, either due to a corticotroph adenoma or in response to primary adrenal insufficiency.

Educational objective:
Pituitary tumors can present with headaches, bitemporal hemianopsia, and hypopituitarism; the most common hormonally active (functional) adenomas are prolactin-secreting adenomas (prolactinomas). Prolactinomas can cause galactorrhea and amenorrhea in women. In men, they often present with hypogonadism.

References

- Progress in the diagnosis and classification of pituitary adenomas.

Pathophysiology	Endocrine, Diabetes & Metabolism	Pituitary adenoma
Subject	System	Topic

Copyright © UWorld. All rights reserved.

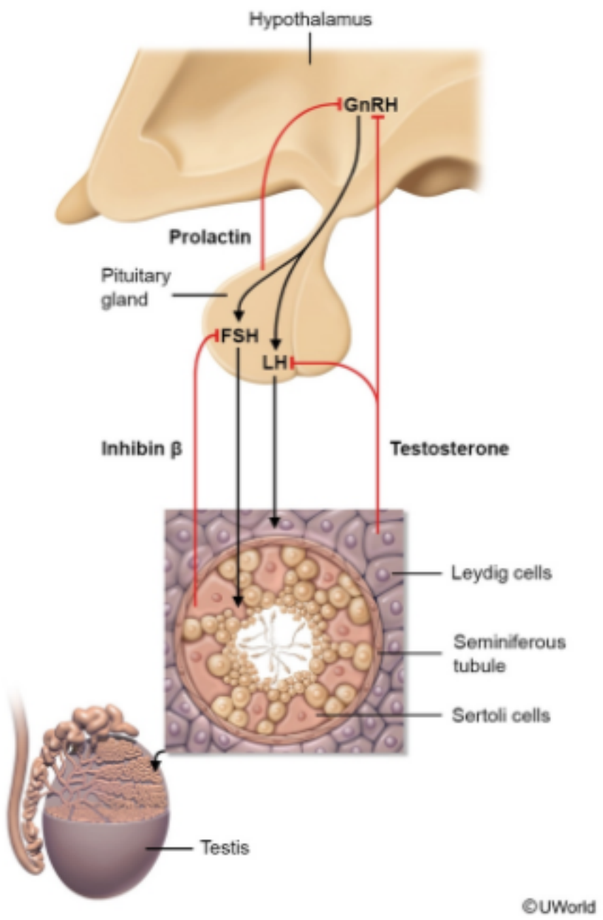
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40

Thyrotroph

Thyrotoxicosis

Exhibit Display

Prolactin and gonadotropin production



Zoom In | Zoom Out | Reset | Add To New Card | Existing Card

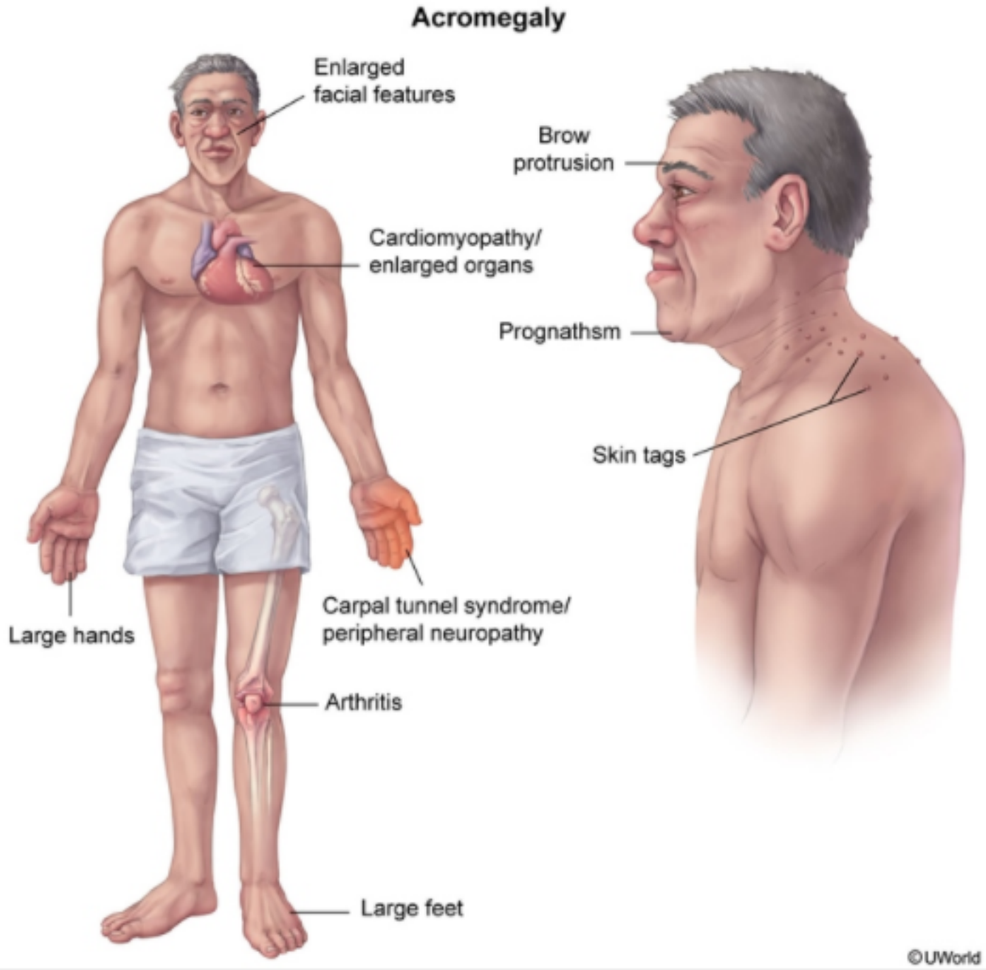
Pituitary tumors can present with headaches, bitemporal hemianopsia, and hypopituitarism; the most common hormonally active (functional)

10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40

Thyrotroph

Thyrotoxicosis

Exhibit Display



Zoom In | Zoom Out | Reset | Add To New Card | Existing Card

Pituitary tumors can present with headaches, bitemporal hemianopsia, and hypopituitarism; the most common hormonally active (functional)

10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40

A 13-year-old girl is brought to the physician by her mother for her yearly physical examination. Her temperature is 36.7 C (98 F), blood pressure is 152/91 mm Hg, pulse is 75/min, and respirations are 18/min. Physical examination shows a lack of secondary sexual characteristics and pelvic examination shows a blind vagina. Laboratory studies reveal hypokalemia and low testosterone and estradiol levels. Cytogenetic analysis shows a 46, XY karyotype. Which of the following enzymes is most likely to be deficient in this patient?

A. 21-hydroxylase

B. 17α-hydroxylase

C. 11β-hydroxylase

D. Side chain cleavage enzyme

E. 5α-reductase

Submit

A 13-year-old girl is brought to the physician by her mother for her yearly physical examination. Her temperature is 36.7 C (98 F), blood pressure is 152/91 mm Hg, pulse is 75/min, and respirations are 18/min. Physical examination shows a lack of secondary sexual characteristics and pelvic examination shows a blind vagina. Laboratory studies reveal hypokalemia and low testosterone and estradiol levels. Cytogenetic analysis shows a 46, XY karyotype. Which of the following enzymes is most likely to be deficient in this patient?

- A. 21-hydroxylase (8%)
- ✓ B. 17α-hydroxylase (72%)
- C. 11β-hydroxylase (12%)
- D. Side chain cleavage enzyme (1%)
- E. 5α-reductase (5%)

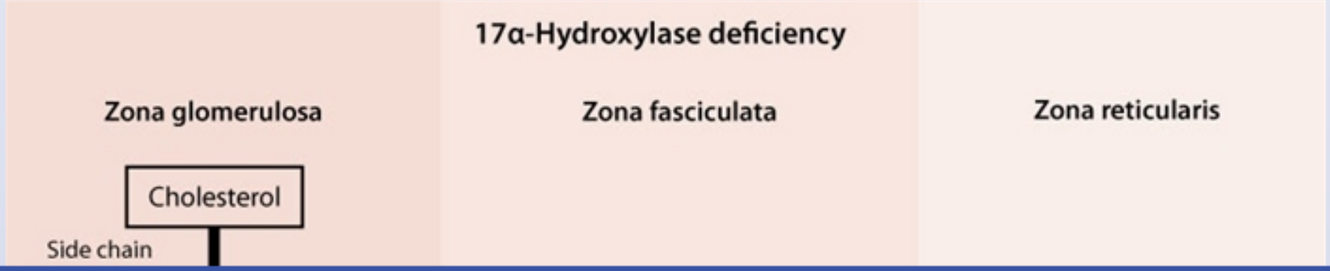
Omitted
Correct answer
B

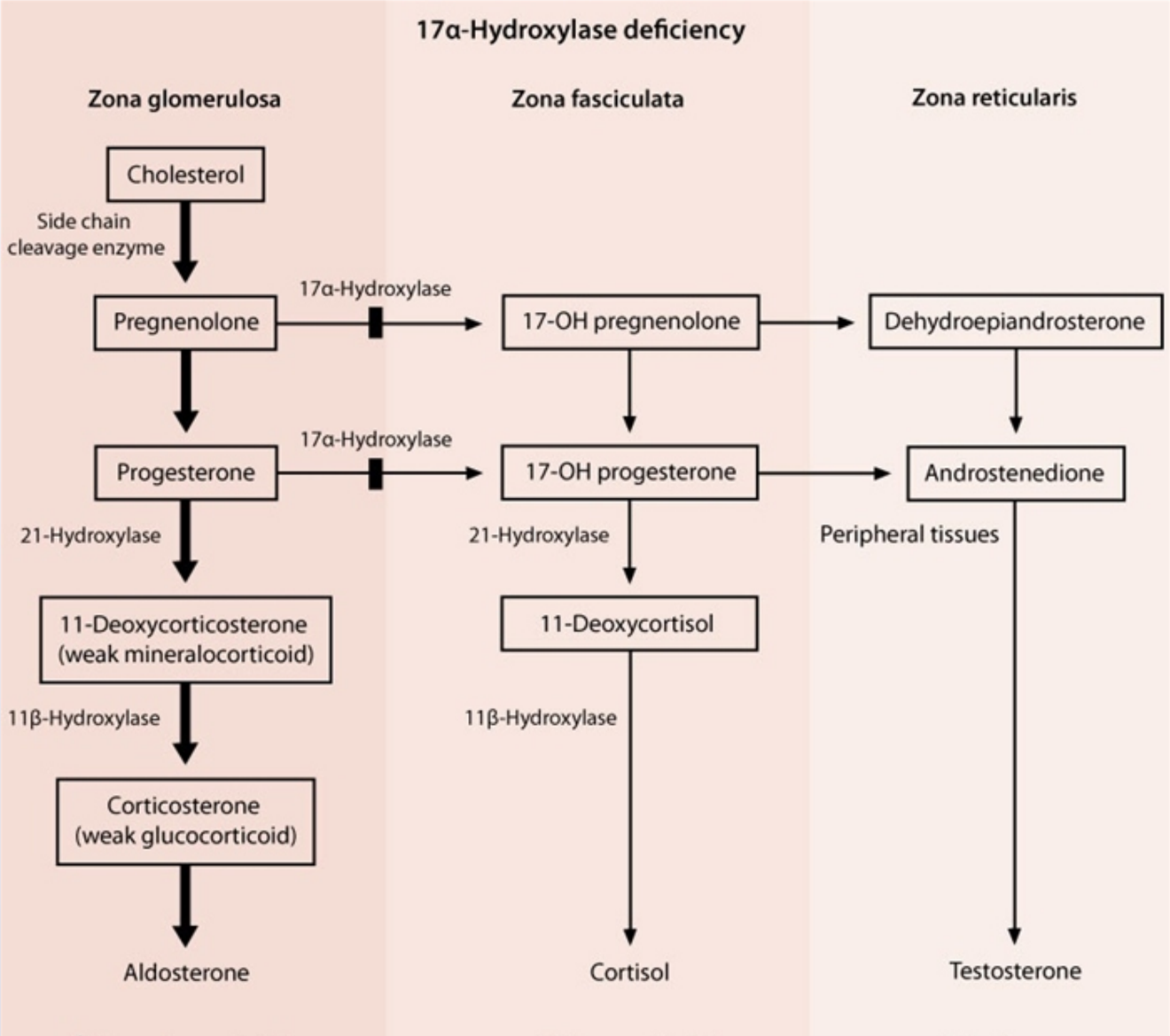
72%
Answered correctly

01 sec
Time Spent

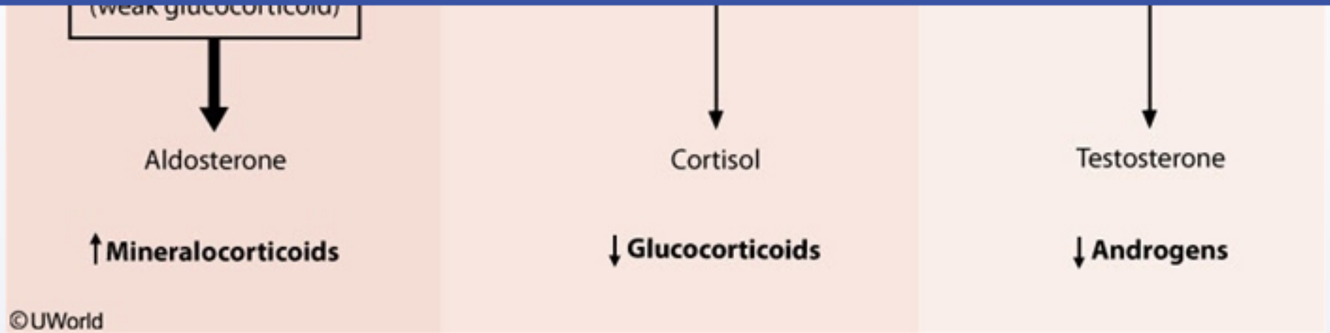
02/04/2020
Last Updated

Explanation




17α-Hydroxylase deficiency
Zona glomerulosa
Zona fasciculata
Zona reticularis
Cholesterol
Side chain cleavage enzyme
Pregnenolone
17α-Hydroxylase
17-OH pregnenolone
Dehydroepiandrosterone
Progesterone
17α-Hydroxylase
17-OH progesterone
Androstenedione
21-Hydroxylase
21-Hydroxylase
Peripheral tissues
11-Deoxycorticosterone (weak mineralocorticoid)
11-Deoxycortisol
11β-Hydroxylase
11β-Hydroxylase
Corticosterone (weak glucocorticoid)
Aldosterone
Cortisol
Testosterone

10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40



This genetically male patient has clinical and laboratory features suggestive of 17α-hydroxylase deficiency, a rare cause of congenital adrenal hyperplasia (CAH) accounting for < 1% of all cases. The 17α-hydroxylase enzyme is active in both the adrenal gland and gonads, where it converts pregnenolone to 17-hydroxypregnenolone and progesterone to 17-hydroxyprogesterone. 17α-hydroxylase deficiency impairs the synthesis of androgens, estrogens, and cortisol but does not inhibit mineralocorticoid production. In fact, the high ACTH levels that result from decreased cortisol production overstimulate the mineralocorticoid pathway, leading to excessive formation of 11-deoxycorticosterone and corticosterone.

Males with 17α-hydroxylase deficiency appear phenotypically female at birth (but lack internal female genitalia) due to the absence of virilizing androgens in utero. However, females develop normal internal and external genitalia. At puberty, impaired synthesis of sex hormones prevents the development of secondary sexual characteristics in both sexes and prevents menarche in females. Excessive production of mineralocorticoids by the adrenals also results in hypertension, hypokalemia, and low renin levels that are usually detected around the time of expected puberty.

(Choice A) 21-hydroxylase deficiency is the most common type of congenital adrenal hyperplasia. Deficiency of 21-hydroxylase decreases glucocorticoid and mineralocorticoid synthesis and increases the production of adrenal androgens. Male infants appear phenotypically normal and frequently develop hypotension and hyperkalemia (salt-wasting).

(Choice C) 11β-hydroxylase deficiency causes decreased glucocorticoid synthesis and increased production of adrenal androgens. Because the production of 11-deoxycorticosterone is also increased, these patients have features of mineralocorticoid excess. Male infants appear phenotypically normal and present with hypertension and hypokalemia.

(Choice D) Side chain cleavage enzyme converts cholesterol to pregnenolone. Because this is the first enzyme in the steroidogenic pathway, deficiency results in impaired synthesis of all steroid hormones. This rare form of CAH also causes cholesterol esters to accumulate in the

©UWorld

This genetically male patient has clinical and laboratory features suggestive of 17α-hydroxylase deficiency, a rare cause of congenital adrenal hyperplasia (CAH) accounting for < 1% of all cases. The 17α-hydroxylase enzyme is active in both the adrenal gland and gonads, where it converts pregnenolone to 17-hydroxypregnenolone and progesterone to 17-hydroxyprogesterone. 17α-hydroxylase deficiency impairs the synthesis of androgens, estrogens, and cortisol but does not inhibit mineralocorticoid production. In fact, the high ACTH levels that result from decreased cortisol production overstimulate the mineralocorticoid pathway, leading to excessive formation of 11-deoxycorticosterone and corticosterone.

Males with 17α-hydroxylase deficiency appear phenotypically female at birth (but lack internal female genitalia) due to the absence of virilizing androgens in utero. However, females develop normal internal and external genitalia. At puberty, impaired synthesis of sex hormones prevents the development of secondary sexual characteristics in both sexes and prevents menarche in females. Excessive production of mineralocorticoids by the adrenals also results in hypertension, hypokalemia, and low renin levels that are usually detected around the time of expected puberty.

(Choice A) 21-hydroxylase deficiency is the most common type of congenital adrenal hyperplasia. Deficiency of 21-hydroxylase decreases glucocorticoid and mineralocorticoid synthesis and increases the production of adrenal androgens. Male infants appear phenotypically normal and frequently develop hypotension and hyperkalemia (salt-wasting).

(Choice C) 11β-hydroxylase deficiency causes decreased glucocorticoid synthesis and increased production of adrenal androgens. Because the production of 11-deoxycorticosterone is also increased, these patients have features of mineralocorticoid excess. Male infants appear phenotypically normal and present with hypertension and hypokalemia.

(Choice D) Side chain cleavage enzyme converts cholesterol to pregnenolone. Because this is the first enzyme in the steroidogenic pathway, deficiency results in impaired synthesis of all steroid hormones. This rare form of CAH also causes cholesterol esters to accumulate in the adrenals and gonads, leading to progressive damage.

(Choice E) 5α-reductase deficiency results in defective conversion of testosterone to dihydrotestosterone, the hormone responsible for fusion of the labial folds during male fetal development. Affected males have ambiguous genitalia at birth but develop normal secondary sexual characteristics (eg, increased muscle mass and phallus enlargement) at puberty as these features are dependent on testosterone.

Educational objective:
17α-hydroxylase deficiency impairs the synthesis of androgens, estrogens, and cortisol but does not inhibit mineralocorticoid production. Boys

10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40

A 29-year-old man comes to the office due to progressive headaches, fatigue, and visual disturbances for the past 6 weeks. He was diagnosed with sarcoidosis a year ago after having a dry cough and hypercalcemia. The patient's condition was treated with oral glucocorticoid therapy, which was discontinued after 6 months due to improvement in symptoms. Physical examination reveals bitemporal defects on visual field testing but is otherwise normal. Laboratory studies again show mild hypercalcemia, but the remainder of the values, including complete blood count, serum glucose, creatinine, and electrolytes, are within normal reference ranges. MRI of the brain reveals a soft tissue mass involving the hypothalamus and pituitary stalk. Which of the following pituitary hormones is most likely elevated in this patient?

A. ACTH
B. Growth hormone
C. Prolactin
D. Thyrotropin
E. Vasopressin

Submit

A 29-year-old man comes to the office due to progressive headaches, fatigue, and visual disturbances for the past 6 weeks. He was diagnosed with sarcoidosis a year ago after having a dry cough and hypercalcemia. The patient's condition was treated with oral glucocorticoid therapy, which was discontinued after 6 months due to improvement in symptoms. Physical examination reveals bitemporal defects on visual field testing but is otherwise normal. Laboratory studies again show mild hypercalcemia, but the remainder of the values, including complete blood count, serum glucose, creatinine, and electrolytes, are within normal reference ranges. MRI of the brain reveals a soft tissue mass involving the hypothalamus and pituitary stalk. Which of the following pituitary hormones is most likely elevated in this patient?

- A. ACTH (13%)
- B. Growth hormone (3%)
- ✓ C. Prolactin (67%)
- D. Thyrotropin (6%)
- E. Vasopressin (8%)

Omitted
Correct answer
C

67%
Answered correctly

02 secs
Time Spent

02/03/2020
Last Updated

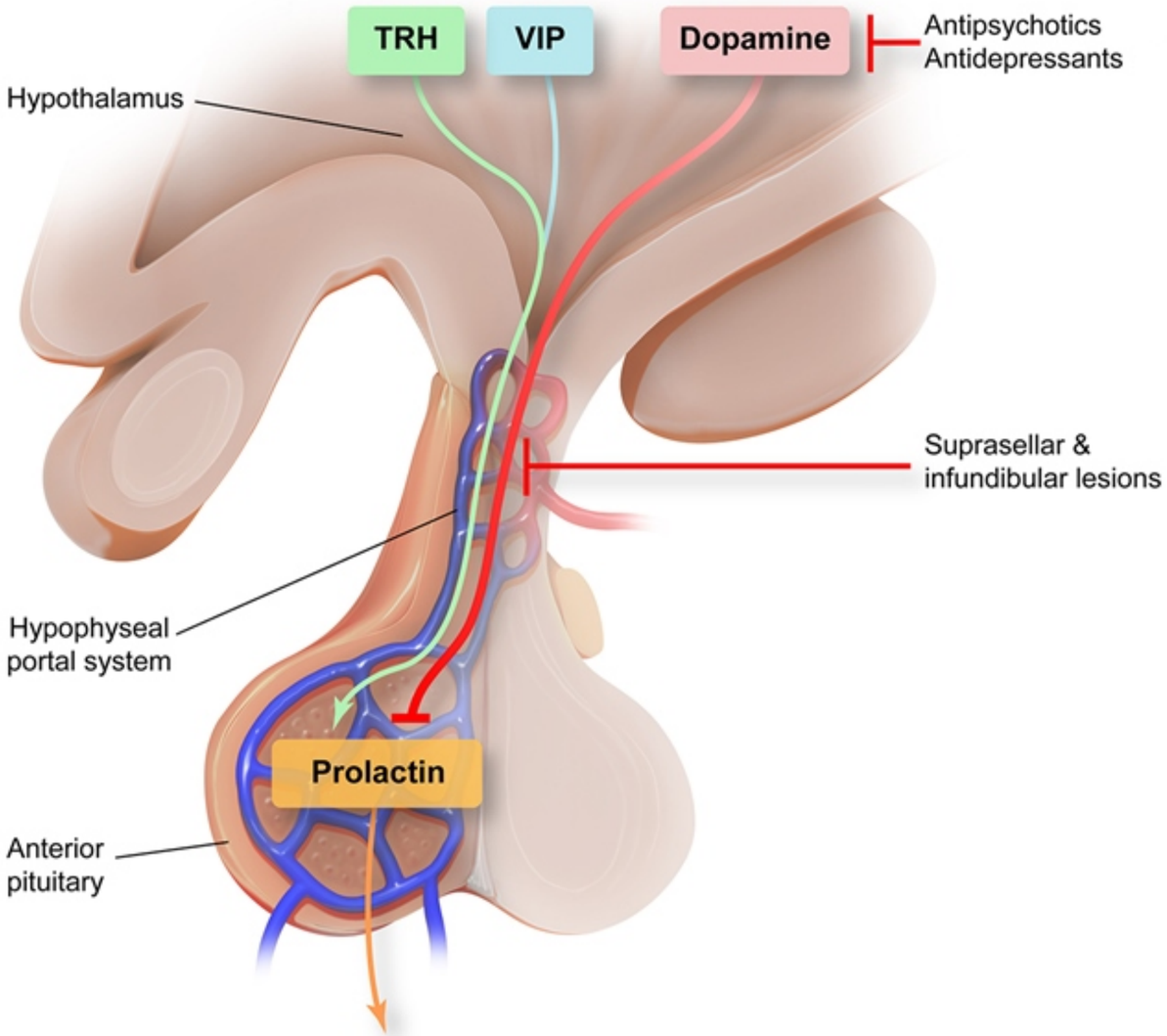
Explanation

Prolactin

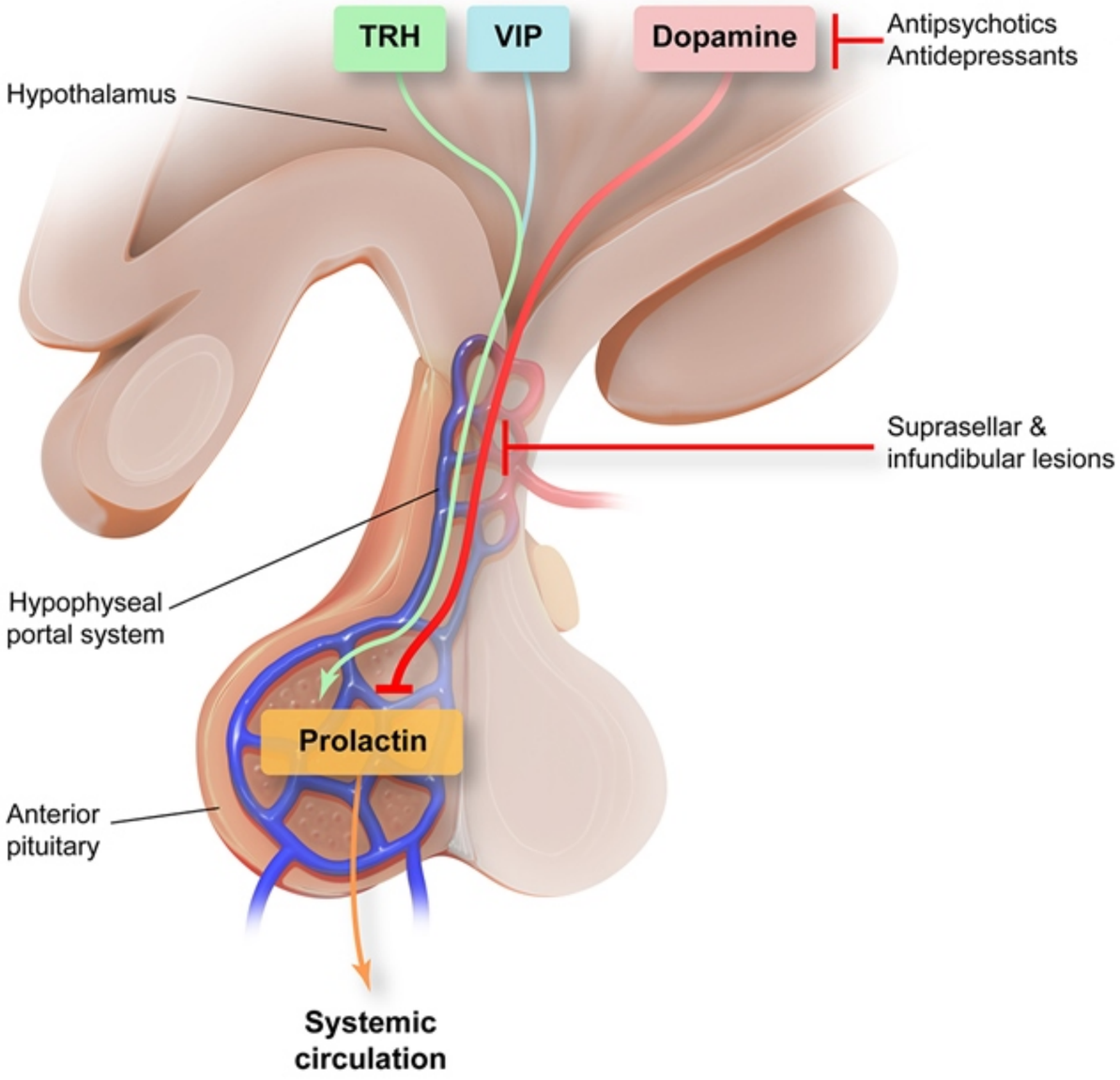
Antipsychotics

10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40

Prolactin



10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40



This patient with **sarcoidosis** has a hypothalamic and pituitary stalk mass with **mass-effect symptoms** (eg, headache, bitemporal visual field defects). In combination with the recurrent hypercalcemia (caused by excessive calcitriol formation by activated macrophages) 6 months after the discontinuation of glucocorticoid therapy, this presentation suggests active sarcoidosis with involvement of the hypothalamus (**neurosarcoidosis**). Although sarcoidosis classically causes noncaseating granulomas involving the lungs, lymph nodes, and skin, granulomas can form in any tissue.

Mass lesions in the hypothalamus or pituitary stalk can disrupt the hypothalamic-pituitary axis by obstructing the hypophyseal portal system. Unlike other pituitary hormones, **prolactin** release is **negatively regulated by dopamine** produced in the hypothalamus. Dopamine acts on the dopamine D2 receptors of lactotrophs, the prolactin-producing cells of the pituitary. Disruption of dopaminergic pathways (eg, by an infiltrating sarcoid lesion) in the pituitary stalk leads to **loss of inhibition** and a subsequent **increase in prolactin**.

(Choices A, B, and D) Pituitary adenomas can cause excess hormone formation; however, this patient has a hypothalamic mass, not a pituitary adenoma. In contrast to prolactin, other pituitary hormones (ACTH, growth hormone, thyrotropin [TSH], LH, and FSH) are inhibited by hypothalamic lesions because the dominant effect of the hypothalamus on them is stimulatory. Although abruptly discontinuing an oral glucocorticoid can cause adrenal insufficiency with a subsequent increase in ACTH, low blood pressure, hypoglycemia, hyponatremia, and hyperkalemia would be expected. In addition, adrenal insufficiency typically occurs rapidly after glucocorticoid withdrawal (not 6 months later).

(Choice E) Vasopressin is produced in the supraoptic and paraventricular nuclei of the hypothalamus and transported to the posterior pituitary for release. Lesions of the hypothalamus and pituitary stalk can decrease vasopressin levels. Mass lesions in the central nervous system can cause vasopressin secretory dysregulation, leading to the syndrome of inappropriate antidiuretic hormone (SIADH) with euvolemic hyponatremia. However, the normal sodium levels in this patient exclude this syndrome.

Educational objective:
The release of prolactin is under inhibitory control by dopamine secretion from the hypothalamus. Disruption of dopaminergic pathways or blockade of dopamine D2 receptors can cause hyperprolactinemia.

Pathophysiology	Endocrine, Diabetes & Metabolism	Hyperprolactinemia
Subject	System	Topic

Copyright © UWorld. All rights reserved.

A 46-year-old woman is hospitalized for recurrent renal colic. She has passed 2 urinary stones during the last 2 years. The most recent stone contained 80% calcium phosphate and 20% calcium oxalate. The patient also has diffuse aches and pains and has a history of peptic ulcer disease, for which she takes famotidine daily. Laboratory results are as follows:

Serum sodium	140 mEq/L
Serum potassium	4.0 mEq/L
Serum chloride	103 mEq/L
Serum creatinine	0.8 mg/dL
Serum calcium	12.0 mg/dL
Serum phosphorus	2.4 mg/dL
24-hour urinary calcium excretion	350 mg (normal: 100-300)

Which of the following changes in bone structure is most likely associated with this patient's condition?

A. Lamellar bone structure resembling a mosaic pattern

B. Osteoid matrix accumulation around trabeculae

C. Spongiosa filling medullary canals with no mature trabeculae

D. Subperiosteal resorption with cortical thinning

E. Trabecular thinning with fewer interconnections

Submit

10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40

Which of the following changes in bone structure is most likely associated with this patient's condition?

A. Lamellar bone structure resembling a mosaic pattern (8%)

B. Osteoid matrix accumulation around trabeculae (6%)

C. Spongiosa filling medullary canals with no mature trabeculae (5%)

✓ D. Subperiosteal resorption with cortical thinning (61%)

E. Trabecular thinning with fewer interconnections (17%)

Omitted
Correct answer
D

61%
Answered correctly

01 sec
Time Spent

02/23/2020
Last Updated

Explanation

This patient with recurrent calcium nephrolithiasis and hypercalcemia most likely has **primary hyperparathyroidism** (PHPT). Besides kidney stones, classic manifestations include bone pain, gastrointestinal disturbances (eg, peptic ulcer disease), and psychiatric symptoms (ie, "bones, stones, abdominal groans, and psychologic moans"). However, asymptomatic hypercalcemia is the most common presentation. 85% of cases are caused by a parathyroid adenoma, but PHPT can also be due to parathyroid hyperplasia or, rarely, parathyroid cancer.

Excess parathyroid hormone causes **hypercalcemia** via the following mechanisms:

- Increased renal tubular Ca^{2+} reabsorption (although most patients have net **hypercalciuria** due to the increased filtered calcium load)
- Increased renal production of 1,25-dihydroxyvitamin D (which in turn increases gastrointestinal Ca^{2+} absorption)
- Increased bone resorption (via osteoclast activation)

This patient with recurrent calcium nephrolithiasis and hypercalcemia most likely has **primary hyperparathyroidism** (PHPT). Besides kidney stones, classic manifestations include bone pain, gastrointestinal disturbances (eg, peptic ulcer disease), and psychiatric symptoms (ie, "bones, stones, abdominal groans, and psychologic moans"). However, asymptomatic hypercalcemia is the most common presentation. 85% of cases are caused by a parathyroid adenoma, but PHPT can also be due to parathyroid hyperplasia or, rarely, parathyroid cancer.

Excess parathyroid hormone causes **hypercalcemia** via the following mechanisms:

- Increased renal tubular Ca^{2+} reabsorption (although most patients have net **hypercalciuria** due to the increased filtered calcium load)
- Increased renal production of 1,25-dihydroxyvitamin D (which in turn increases gastrointestinal Ca^{2+} absorption)
- Increased bone resorption (via osteoclast activation)

Patients usually also have **hypophosphatemia** due to decreased phosphate reabsorption in the proximal renal tubules.

Because of the increased bone resorption, PHPT often leads to **osteoporosis**. However, unlike the typical osteoporosis of aging, which predominantly affects trabecular bone, osteoporosis in PHPT is most pronounced in the **cortical (compact) bone** of the appendicular skeleton (eg, pectoral girdle, pelvic girdle, limbs). Cortical thinning is characteristic and appears radiologically as **subperiosteal erosions**. More advanced disease can present as osteitis fibrosa cystica, characterized by granular decalcification of the skull ("salt-and-pepper skull"), osteolytic cysts, and brown tumors.

(Choice A) Disorganized lamellar bone in a mosaic pattern is a characteristic finding in Paget disease of bone. Serum calcium and phosphorus are normal in these patients.

(Choice B) Osteoid matrix accumulation around trabeculae is seen in vitamin D deficiency. Histologically, there is excessive unmineralized osteoid with widened osteoid seams. Patients typically have low urinary calcium.

(Choice C) Osteopetrosis ("marble bone disease") is characterized by persistence of the primary spongiosa in the medullary cavity with no mature trabeculae. It is caused by decreased osteoclastic bone resorption, resulting in accumulation of woven bone and diffuse skeletal thickening.

(Choice E) Trabecular thinning with fewer interconnections is characteristic of postmenopausal osteoporosis. Although long-standing PHPT causes thinning of cortical bone, the trabecular architecture remains relatively preserved.

Because of the increased bone resorption, PHPT often leads to **osteoporosis**. However, unlike the typical osteoporosis of aging, which predominantly affects trabecular bone, osteoporosis in PHPT is most pronounced in the **cortical (compact) bone** of the appendicular skeleton (eg, pectoral girdle, pelvic girdle, limbs). Cortical thinning is characteristic and appears radiologically as **subperiosteal erosions**. More advanced disease can present as osteitis fibrosa cystica, characterized by granular decalcification of the skull ("salt-and-pepper skull"), osteolytic cysts, and brown tumors.

(Choice A) Disorganized lamellar bone in a mosaic pattern is a characteristic finding in Paget disease of bone. Serum calcium and phosphorus are normal in these patients.

(Choice B) Osteoid matrix accumulation around trabeculae is seen in vitamin D deficiency. Histologically, there is excessive unmineralized osteoid with widened osteoid seams. Patients typically have low urinary calcium.

(Choice C) Osteopetrosis ("marble bone disease") is characterized by persistence of the primary spongiosa in the medullary cavity with no mature trabeculae. It is caused by decreased osteoclastic bone resorption, resulting in accumulation of woven bone and diffuse skeletal thickening.

(Choice E) Trabecular thinning with fewer interconnections is characteristic of postmenopausal osteoporosis. Although long-standing PHPT causes thinning of cortical bone, the trabecular architecture remains relatively preserved.

Educational objective:
Increased bone resorption in primary hyperparathyroidism leads to osteoporosis primarily involving the cortical bone of the appendicular skeleton. The cortical thinning appears radiologically as subperiosteal erosions. More advanced disease can present as osteitis fibrosa cystica (ie, granular decalcification of the skull, osteolytic cysts, and brown tumors).

References

- Radiographical appearance of osteitis fibrosa cystica in primary hyperparathyroidism before and after parathyroidectomy.

Pathophysiology	Endocrine, Diabetes & Metabolism	Hyperparathyroidism
Subject	System	Topic

Copyright © UWorld. All rights reserved.

10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40

A group of investigators is studying osteoprotegerin function in patients with postmenopausal osteoporosis. Using an engineered mouse strain, they develop a chimeric monoclonal antibody that blocks binding of receptor activator of nuclear factor kappa B (RANK) to RANK ligand (RANK-L). The investigators inject this monoclonal antibody into human subjects. Eight weeks later, a bone biopsy is obtained from all subjects. Which of the following is the most likely observed finding?

A. Decreased bone mineralization
B. Decreased bone resorption
C. Increased osteoblast activity
D. Increased osteoclast activity
E. Increased survival of osteocytes

Submit

A group of investigators is studying osteoprotegerin function in patients with postmenopausal osteoporosis. Using an engineered mouse strain, they develop a chimeric monoclonal antibody that blocks binding of receptor activator of nuclear factor kappa B (RANK) to RANK ligand (RANK-L). The investigators inject this monoclonal antibody into human subjects. Eight weeks later, a bone biopsy is obtained from all subjects. Which of the following is the most likely observed finding?

- A. Decreased bone mineralization (2%)
- ✓ B. Decreased bone resorption (80%)
- C. Increased osteoblast activity (8%)
- D. Increased osteoclast activity (6%)
- E. Increased survival of osteocytes (2%)

Omitted
Correct answer
B

80%
Answered correctly

01 sec
Time Spent

02/18/2020
Last Updated

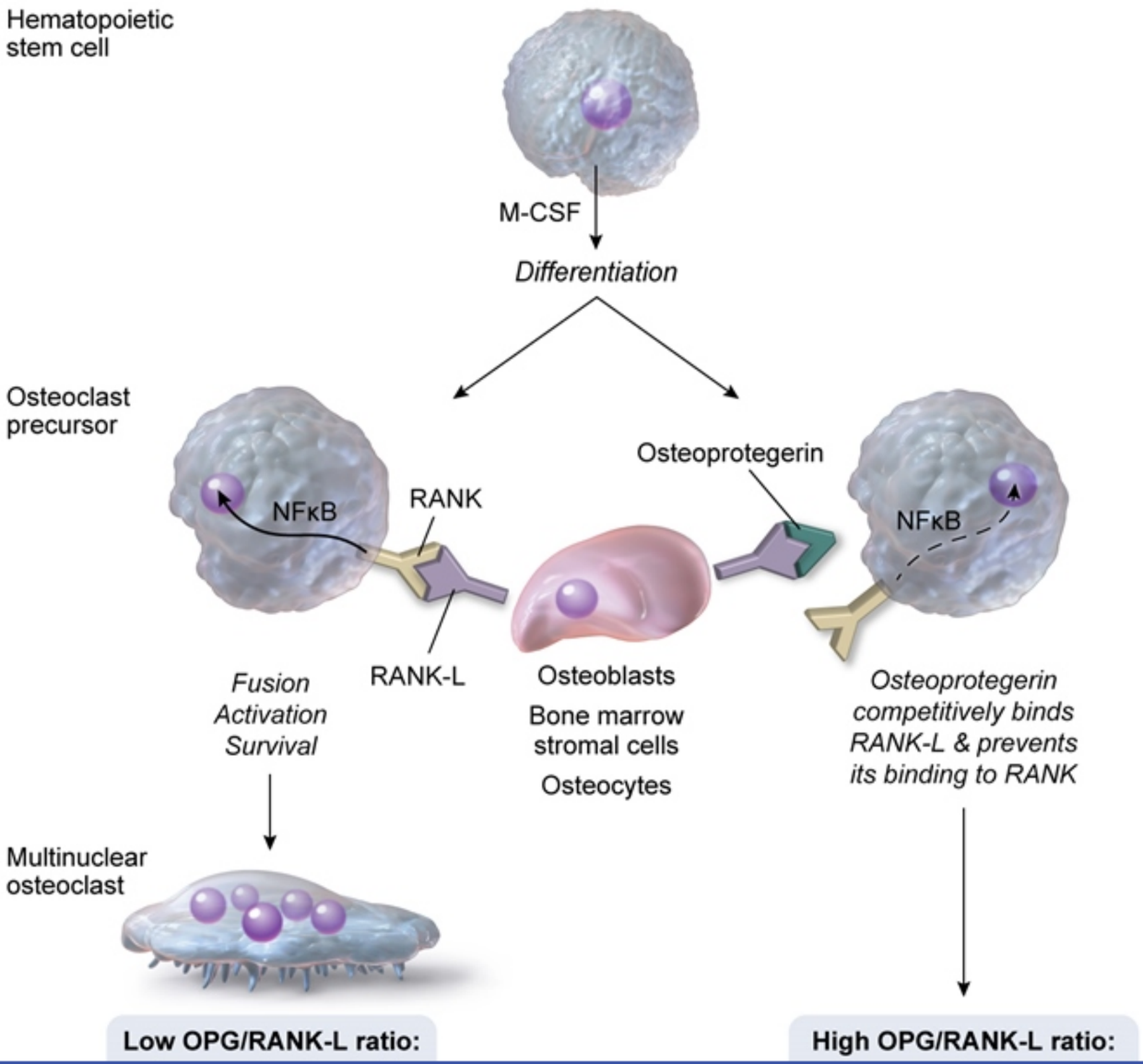
Explanation

Osteoclast differentiation

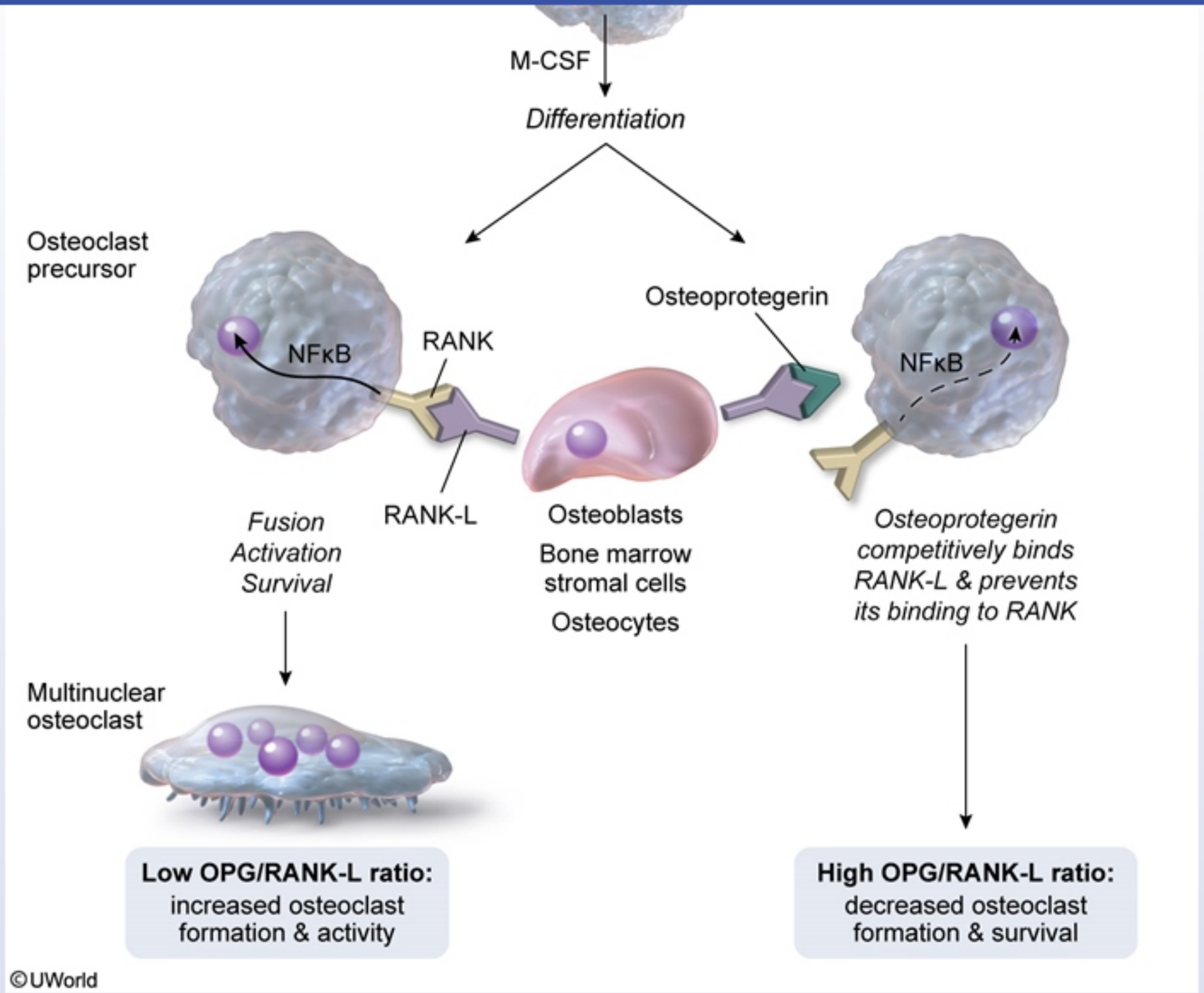
Hematopoietic
stem cell

10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40

Osteoclast differentiation



10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40



Interaction between the receptor for activated nuclear factor kappa B (**RANK**) and its ligand (**RANK-L**), is critical for the development of mature, multinucleated osteoclasts. This **binding is blocked by osteoprotegerin** (OPG), which acts as a decoy receptor for RANK-L (preventing it from

©UWorld

Interaction between the receptor for activated nuclear factor kappa B (**RANK**) and its ligand (**RANK-L**), is critical for the development of mature, multinucleated osteoclasts. This **binding is blocked by osteoprotegerin** (OPG), which acts as a decoy receptor for RANK-L (preventing it from interacting with RANK). By binding RANK-L, OPG reduces the differentiation and survival of osteoclasts, resulting in decreased bone resorption and **increased bone density**.

Estrogen maintains bone mass in premenopausal women by inducing production of OPG by osteoblasts and stromal cells and decreasing expression of RANK on osteoclast precursors. The **loss of OPG at menopause** leads to increased osteoclast activity that predisposes to **osteoporosis**.

Denosumab is a monoclonal antibody used in the treatment of postmenopausal osteoporosis. It **works similar to OPG** in that it binds RANK-L and prevents its interaction with RANK receptor. Denosumab therefore causes decreased osteoclast differentiation and activity **(Choice D)** as well as **decreased bone resorption**.

(Choices A and C) RANK (receptor) is not present on osteoblasts, and inhibition of binding of RANK-L to RANK does not affect osteoblast activity or bone mineralization.

(Choice E) Osteocytes are derived from osteoblasts. Osteocyte survival is regulated by a variety of factors including mechanical stress, local growth factors, and steroid hormone levels. Although osteocytes produce RANK-L, which acts on osteoclasts, osteocyte survival is not dependent on the RANK signaling pathway.

Educational objective:
The nuclear factor kappa B (RANK)/RANK-ligand (RANK-L) interaction is essential for the formation and differentiation of osteoclasts. Osteoprotegerin (OPG) blocks binding of RANK-L to RANK and reduces formation of mature osteoclasts, leading to decreased bone resorption. Denosumab is a monoclonal antibody used in the treatment of postmenopausal osteoporosis that works in a manner similar to OPG.

References

- Prevention and treatment of postmenopausal osteoporosis.

Pathophysiology	Endocrine, Diabetes & Metabolism	Osteoporosis
Subject	System	Topic

10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40

A 15-year-old boy comes to the office for evaluation of a neck mass. The patient first noticed the mass a month ago and it has progressively enlarged. He has had no neck pain, fever, or difficulty swallowing or breathing. Examination shows a firm, nontender mass affecting the left thyroid lobe. TSH is within normal limits. Ultrasonography reveals a hypoechoic 2-cm nodule in the upper portion of the left thyroid lobe. Fine-needle biopsy reveals a cluster of large cells with abundant cytoplasm that stain positive for calcitonin. The patient is also found to be positive for a germline *RET* mutation. A total thyroidectomy is planned. Prior to the surgery, additional testing should be performed to evaluate for an abnormality in which of the following organs?

A. Adrenal cortex
B. Adrenal medulla
C. Anterior pituitary
D. Pancreatic islets
E. Thymus

Submit

A 15-year-old boy comes to the office for evaluation of a neck mass. The patient first noticed the mass a month ago and it has progressively enlarged. He has had no neck pain, fever, or difficulty swallowing or breathing. Examination shows a firm, nontender mass affecting the left thyroid lobe. TSH is within normal limits. Ultrasonography reveals a hypoechoic 2-cm nodule in the upper portion of the left thyroid lobe. Fine-needle biopsy reveals a cluster of large cells with abundant cytoplasm that stain positive for calcitonin. The patient is also found to be positive for a germline *RET* mutation. A total thyroidectomy is planned. Prior to the surgery, additional testing should be performed to evaluate for an abnormality in which of the following organs?

- A. Adrenal cortex (3%)
- ✓ B. Adrenal medulla (82%)
- C. Anterior pituitary (5%)
- D. Pancreatic islets (6%)
- E. Thymus (1%)

Omitted
Correct answer
B

82%
Answered correctly

01 sec
Time Spent

05/09/2020
Last Updated

Explanation

Multiple endocrine neoplasia type 2	
Inheritance	• Autosomal dominant • Germ-line activating mutations of *RET*

Multiple endocrine neoplasia type 2	
Inheritance	• Autosomal dominant • Germ-line activating mutations of *RET* proto-oncogene
Type 2A	• Medullary thyroid cancer (>95%) • Pheochromocytoma • Parathyroid hyperplasia
Type 2B	• Medullary thyroid cancer (>95%) • Pheochromocytoma • Mucosal neuromas, marfanoid habitus

This patient has **medullary thyroid cancer** (MTC), a neuroendocrine malignancy arising from the calcitonin-secreting parafollicular C cells. Most cases of MTC are sporadic, but approximately 20% are familial, due to germline mutations of the ***RET* proto-oncogene**. Multiple endocrine neoplasia type 2 (**MEN2**) is the most common inherited disorder associated with activating *RET* mutations, and is characterized by:

- MTC
- Pheochromocytoma
- Parathyroid hyperplasia (type 2A) or marfanoid habitus (tall, slender build, increased limb to height ratio) and mucosal neuromas (type 2B)

Pheochromocytoma is a catecholamine-secreting neoplasm arising from the chromaffin cells of the **adrenal medulla**. Up to 50% of patients with MEN2 develop pheochromocytoma. In patients with undiagnosed pheochromocytoma, induction of anesthesia can precipitate a catecholamine (epinephrine and norepinephrine) surge, leading to hypertensive crisis, flash pulmonary edema, and atrial fibrillation. Therefore, patients who have MTC associated with germline *RET* mutations should be screened for pheochromocytoma (eg, 24-hour assay for urinary metanephrines and catecholamines) prior to surgery.

(Choices A, C, D and E) MEN1 is characterized by anterior pituitary adenomas, primary hyperparathyroidism (due to parathyroid adenomas or hyperplasia), and neuroendocrine tumors of the pancreas and gastrointestinal tract (eg, gastrinoma, insulinoma). A number of other tumors are also more frequent in MEN1, including adrenocortical adenomas and neuroendocrine thymomas (thymic carcinoid). However, MEN1 is due to mutations in the *MEN1* gene (not *RET*) and is not associated with MTC.

neoplasia type 2 (**MEN2**) is the most common inherited disorder associated with activating *RET* mutations, and is characterized by:

- MTC
- Pheochromocytoma
- Parathyroid hyperplasia (type 2A) or marfanoid habitus (tall, slender build, increased limb to height ratio) and mucosal neuromas (type 2B)

Pheochromocytoma is a catecholamine-secreting neoplasm arising from the chromaffin cells of the **adrenal medulla**. Up to 50% of patients with MEN2 develop pheochromocytoma. In patients with undiagnosed pheochromocytoma, induction of anesthesia can precipitate a catecholamine (epinephrine and norepinephrine) surge, leading to hypertensive crisis, flash pulmonary edema, and atrial fibrillation. Therefore, patients who have MTC associated with germline *RET* mutations should be screened for pheochromocytoma (eg, 24-hour assay for urinary metanephrines and catecholamines) prior to surgery.

(Choices A, C, D and E) MEN1 is characterized by anterior pituitary adenomas, primary hyperparathyroidism (due to parathyroid adenomas or hyperplasia), and neuroendocrine tumors of the pancreas and gastrointestinal tract (eg, gastrinoma, insulinoma). A number of other tumors are also more frequent in MEN1, including adrenocortical adenomas and neuroendocrine thymomas (thymic carcinoid). However, MEN1 is due to mutations in the *MEN1* gene (not *RET*) and is not associated with MTC.

Educational objective:
Multiple endocrine neoplasia type 2 is caused by germline activating mutations in the *RET* proto-oncogene and frequently results in both medullary thyroid cancer and pheochromocytoma. In patients with undiagnosed pheochromocytoma, induction of anesthesia (eg, preparation for thyroidectomy) can precipitate a catecholamine surge, leading to hypertensive crisis, flash pulmonary edema, and atrial fibrillation.

References

- The North American Neuroendocrine Tumor Society consensus guideline for the diagnosis and management of neuroendocrine tumors: pheochromocytoma, paraganglioma, and medullary thyroid cancer.

Pathophysiology	Endocrine, Diabetes & Metabolism	Multiple endocrine neoplasia
Subject	System	Topic

Copyright © UWorld. All rights reserved.

A 20-year-old woman with cystic fibrosis comes to the clinic for routine follow-up. She has no concerns since her last visit 3 months ago. Vital signs are normal. Examination shows a hyperexpanded chest with equal aeration bilaterally. Fasting glucose level is 90 mg/dL. Plasma glucose level 2 hours after oral glucose tolerance testing is 185 mg/dL (normal: <140). Which of the following is the primary mechanism responsible for this patient's abnormal test result?

A. Decreased insulin production due to disruption of pancreatic islet cells

B. Decreased insulin production due to pancreatic islet cell autoantibodies

C. Increased glucagon secretion due to chronic malnutrition

D. Increased insulin degradation due to hypermetabolic needs

E. Increased insulin resistance from chronic stimulation by cortisol and epinephrine

Submit

A 20-year-old woman with cystic fibrosis comes to the clinic for routine follow-up. She has no concerns since her last visit 3 months ago. Vital signs are normal. Examination shows a hyperexpanded chest with equal aeration bilaterally. Fasting glucose level is 90 mg/dL. Plasma glucose level 2 hours after oral glucose tolerance testing is 185 mg/dL (normal: <140). Which of the following is the primary mechanism responsible for this patient's abnormal test result?

- ✓ A. Decreased insulin production due to disruption of pancreatic islet cells (100%)
- B. Decreased insulin production due to pancreatic islet cell autoantibodies (0%)
- C. Increased glucagon secretion due to chronic malnutrition (0%)
- D. Increased insulin degradation due to hypermetabolic needs (0%)
- E. Increased insulin resistance from chronic stimulation by cortisol and epinephrine (0%)

Omitted
Correct answer
A

Collecting Statistics

02 secs
Time Spent

07/08/2020
Last Updated

Explanation

Cystic fibrosis (CF) is an autosomal recessive disorder caused by a mutation (eg, ΔF508) in the gene encoding the CF transmembrane conductance regulator (CFTR) protein. CFTR normally regulates the transport of chloride ions across secretory epithelial cells; a defect in this protein leads to the accumulation of **thick, inspissated secretions** in ducts throughout the body (eg, lungs, pancreas, gastrointestinal tract, vas deferens).

In the pancreas, dehydrated, viscous secretions block the lumen of the **pancreatic ducts**, causing both **exocrine** (ie, malabsorption) and **endocrine dysfunction**. Endocrine dysfunction is due to pancreatic fibrosis and fat infiltration, which cause progressive encroachment,

Explanation

Cystic fibrosis (CF) is an autosomal recessive disorder caused by a mutation (eg, ΔF508) in the gene encoding the CF transmembrane conductance regulator (CFTR) protein. CFTR normally regulates the transport of chloride ions across secretory epithelial cells; a defect in this protein leads to the accumulation of **thick, inspissated secretions** in ducts throughout the body (eg, lungs, pancreas, gastrointestinal tract, vas deferens).

In the pancreas, dehydrated, viscous secretions block the lumen of the **pancreatic ducts**, causing both **exocrine** (ie, malabsorption) and **endocrine dysfunction**. Endocrine dysfunction is due to pancreatic fibrosis and fat infiltration, which cause progressive encroachment, disruption, and **destruction of pancreatic islet cells**. This injury results in **decreased insulin production** and **CF-related diabetes** (CFRD). In the initial stages, glucose is typically normal when fasting (ie, able to produce some insulin) but elevated after a glycemic load, as seen in this patient. As the disease progresses, there is fasting hyperglycemia and increasing hemoglobin A1c levels.

Because early diagnosis and treatment with insulin are associated with improved pulmonary status and overall survival, all CF patients should undergo regular screening with oral glucose tolerance tests.

(Choice B) Decreased insulin production due to pancreatic islet cell autoantibodies describes the pathogenesis of type 1 diabetes mellitus. Islet cell destruction in CFRD is not an autoimmune process.

(Choice C) Although glucagon increases in response to starvation, chronic malnutrition is likely to result in glucagon resistance. In addition, glucagon-producing alpha islet cells are damaged along with beta cells in patients with CF, resulting in decreased glucagon secretion.

(Choices D and E) Stress-induced hyperglycemia and insulin resistance can occur in times of acutely increased metabolic demand (eg, trauma, burn, sepsis) due to the release of cortisol, epinephrine, and glucagon. Patients with late-stage CFRD may have a component of insulin resistance during times of acute stress and inflammation (eg, pulmonary exacerbation); however, this is not the primary mechanism of CFRD.

Educational objective:
Cystic fibrosis (CF) causes the accumulation of thick, viscous secretions in ducts throughout the body. CF-related diabetes occurs after the progressive destruction of pancreatic islet cells leads to decreased insulin production.

References

Cystic fibrosis-related diabetes: pathophysiology, screening and diagnosis

In the pancreas, dehydrated, viscous secretions block the lumen of the **pancreatic ducts**, causing both **exocrine** (ie, malabsorption) and **endocrine dysfunction**. Endocrine dysfunction is due to pancreatic fibrosis and fat infiltration, which cause progressive encroachment, disruption, and **destruction of pancreatic islet cells**. This injury results in **decreased insulin production** and **CF-related diabetes** (CFRD). In the initial stages, glucose is typically normal when fasting (ie, able to produce some insulin) but elevated after a glycemic load, as seen in this patient. As the disease progresses, there is fasting hyperglycemia and increasing hemoglobin A1c levels.

Because early diagnosis and treatment with insulin are associated with improved pulmonary status and overall survival, all CF patients should undergo regular screening with oral glucose tolerance tests.

(Choice B) Decreased insulin production due to pancreatic islet cell autoantibodies describes the pathogenesis of type 1 diabetes mellitus. Islet cell destruction in CFRD is not an autoimmune process.

(Choice C) Although glucagon increases in response to starvation, chronic malnutrition is likely to result in glucagon resistance. In addition, glucagon-producing alpha islet cells are damaged along with beta cells in patients with CF, resulting in decreased glucagon secretion.

(Choices D and E) Stress-induced hyperglycemia and insulin resistance can occur in times of acutely increased metabolic demand (eg, trauma, burn, sepsis) due to the release of cortisol, epinephrine, and glucagon. Patients with late-stage CFRD may have a component of insulin resistance during times of acute stress and inflammation (eg, pulmonary exacerbation); however, this is not the primary mechanism of CFRD.

Educational objective:
Cystic fibrosis (CF) causes the accumulation of thick, viscous secretions in ducts throughout the body. CF-related diabetes occurs after the progressive destruction of pancreatic islet cells leads to decreased insulin production.

References

- Cystic fibrosis related diabetes: pathophysiology, screening and diagnosis.

Pathophysiology	Endocrine, Diabetes & Metabolism	Cystic fibrosis
Subject	System	Topic

Copyright © UWorld. All rights reserved.

Omitted
Correct answer
A

Explanation

Cystic fibrosis (CF) is an a
conductance regulator (CF
protein leads to the accum
deferens).

In the pancreas, dehydrat
endocrine dysfunction.
disruption, and **destructio**
the initial stages, glucose
patient. As the disease pr

Because early diagnosis a
undergo regular screening

(Choice B) Decreased in
cell destruction in CFRD is

(Choice C) Although gluc
glucagon-producing alpha

(Choices D and E) Stress-induced hyperglycemia and insulin resistance can occur in times of acutely increased metabolic demand (eg, trauma, burn, sepsis) due to the release of cortisol, epinephrine, and glucagon. Patients with late-stage CFRD may have a component of insulin

Exhibit Display

Features of cystic fibrosis	

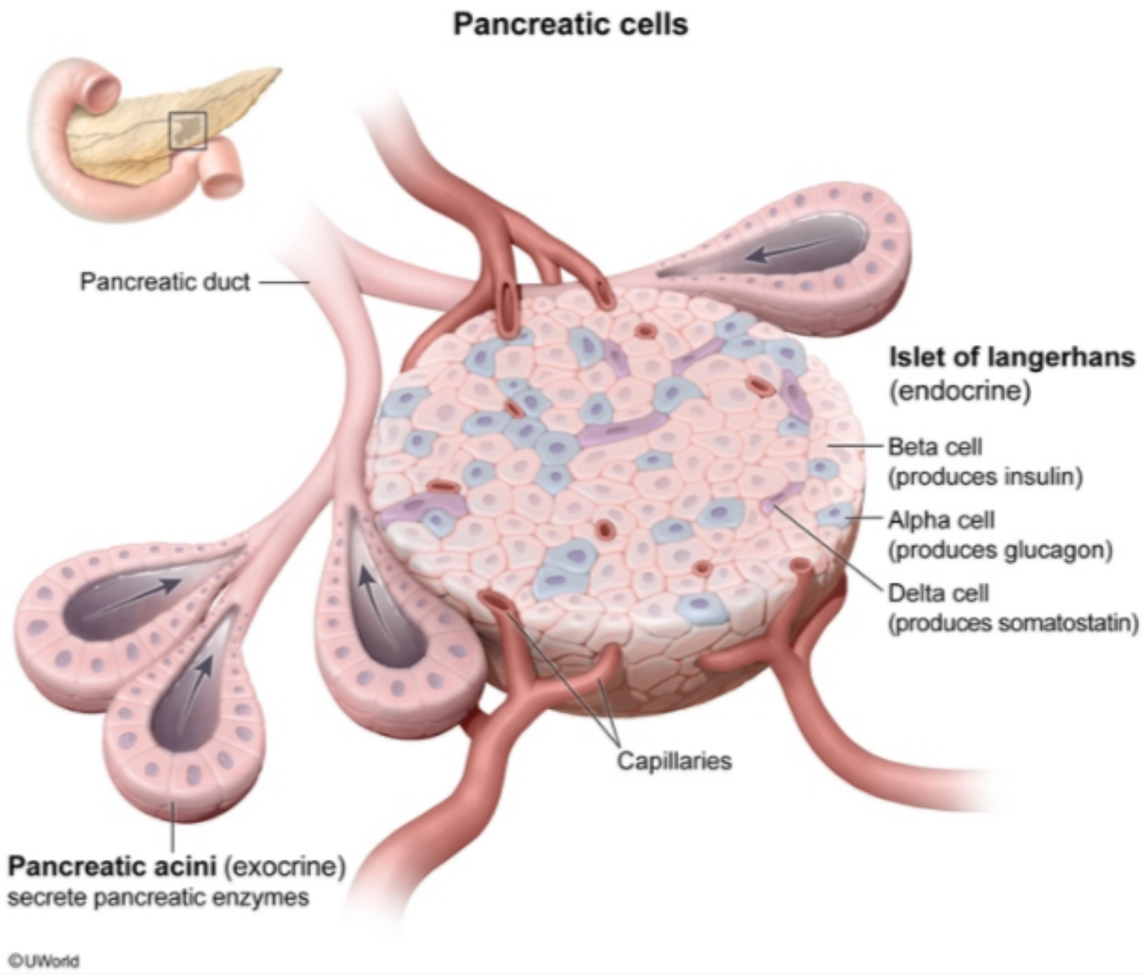
Pathogenesis	• Autosomal recessive mutation (ΔF508) impairs CFTR function
	• Decreased water content causes thick, viscous mucus:
	  ◦ Chronic airway obstruction
	  ◦ Gastrointestinal malabsorption

Clinical manifestations	• Chronic, productive cough • Recurrent sinopulmonary infections (especially *Staphylococcus aureus* & *Pseudomonas aeruginosa*) • Pancreatic insufficiency • Male infertility (bilateral absence of vas deferens)
Diagnosis	• Elevated sweat chloride levels • Nasal potential difference measurements • Genetic testing for *CFTR* mutations
CFTR = cystic fibrosis transmembrane conductance regulator.	

Add To Flash Card

10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40

Exhibit Display



Zoom In Zoom Out Reset Add To Flash Card

burn, sepsis) due to the release of cortisol, epinephrine, and glucagon. Patients with late-stage CFRD may have a component of insulin

A 27-year-old man comes to the office for an infertility evaluation. He and his wife have been trying to conceive for the last 16 months. A previous evaluation of his wife showed no abnormalities. The patient has no prior medical conditions and takes no medications. Height is 188 cm (6' 2") and weight is 75 kg (165.3 lb). BMI is 21 kg/m^2. On physical examination, heart and lung sounds are normal. There is bilateral gynecomastia, and genital examination shows small, firm testes. The lower extremities appear abnormally long. Further evaluation will most likely show which of the following sets of findings in this patient?

	Serum LH	Serum FSH	Serum testosterone	Sperm count
A.	Decreased	Decreased	Decreased	Decreased
B.	Normal	Normal	Normal	Absent
C.	Decreased	Normal	Increased	Decreased
D.	Increased	Increased	Decreased	Absent
E.	Normal	Increased	Normal	Decreased

Submit

A 27-year-old man comes to the office for an infertility evaluation. He and his wife have been trying to conceive for the last 16 months. A previous evaluation of his wife showed no abnormalities. The patient has no prior medical conditions and takes no medications. Height is 188 cm (6' 2") and weight is 75 kg (165.3 lb). BMI is 21 kg/m^2. On physical examination, heart and lung sounds are normal. There is bilateral gynecomastia, and genital examination shows small, firm testes. The lower extremities appear abnormally long. Further evaluation will most likely show which of the following sets of findings in this patient?

	Serum LH	Serum FSH	Serum testosterone	Sperm count
A.	Decreased (21%)	Decreased	Decreased	Decreased
B.	Normal (1%)	Normal	Normal	Absent
C.	Decreased (2%)	Normal	Increased	Decreased
✓ D.	Increased (68%)	Increased	Decreased	Absent
E.	Normal (5%)	Increased	Normal	Decreased

Omitted
Correct answer
D

68%
Answered correctly

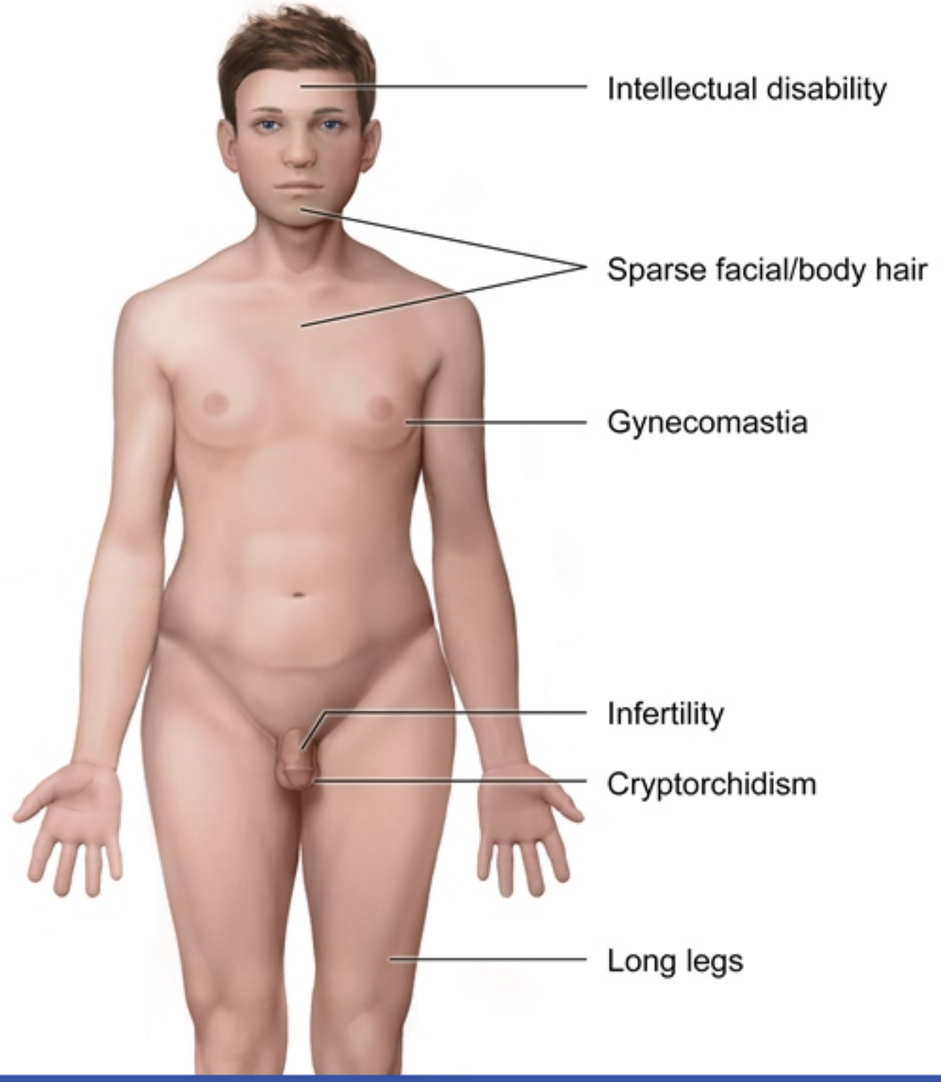
02 secs
Time Spent

06/06/2020
Last Updated

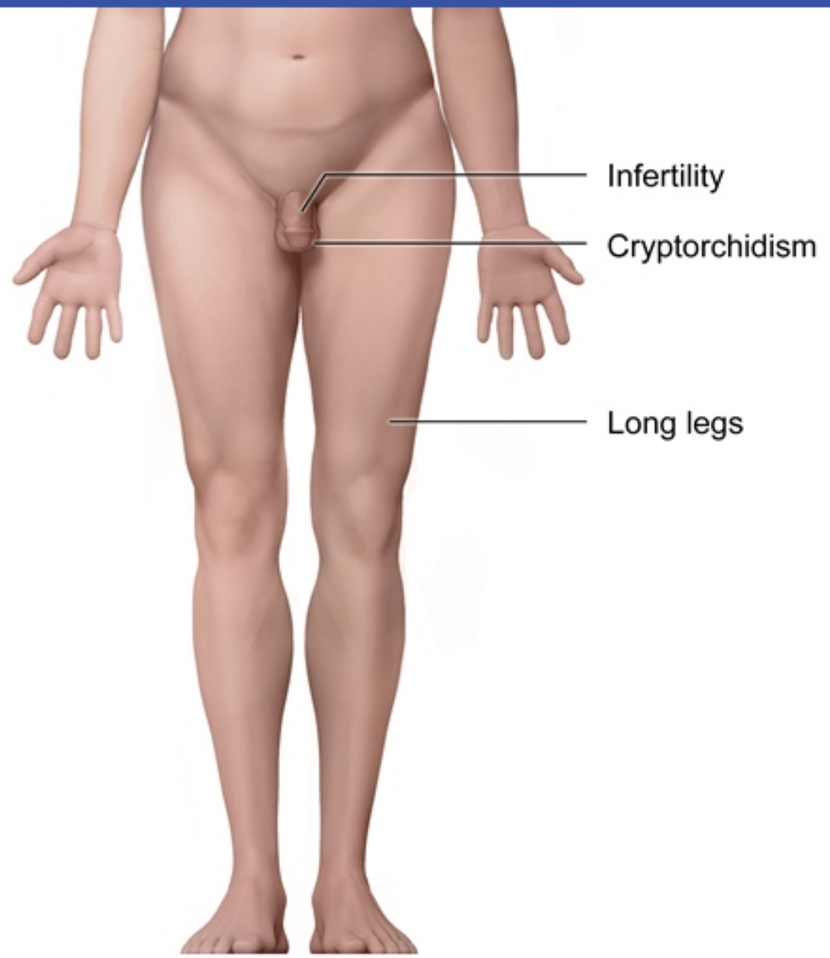
Explanation

10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40

Klinefelter syndrome (47,XXY)



10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40



©UWorld

This patient has infertility, **gynecomastia**, and **long lower extremities**, findings which together are highly suggestive of **Klinefelter syndrome**. Klinefelter syndrome is a chromosomal disorder (47,XXY) that can lead to **azoospermia** and infertility, although individuals with mosaic variants may have variable degrees of spermatogenesis. Common nonreproductive manifestations include intellectual and language impairment.

Klinefelter syndrome is the most common cause of male hypogonadism and is characterized by progressive destruction and hyalinization of the seminiferous tubules, leading to small, firm testes. Serum **inhibin levels are decreased** as a result of the Sertoli cell damage; Leydig cells are

This patient has infertility, **gynecomastia**, and **long lower extremities**, findings which together are highly suggestive of **Klinefelter syndrome**. Klinefelter syndrome is a chromosomal disorder (47,XXY) that can lead to **azoospermia** and infertility, although individuals with mosaic variants may have variable degrees of spermatogenesis. Common nonreproductive manifestations include intellectual and language impairment.

Klinefelter syndrome is the most common cause of male hypogonadism and is characterized by progressive destruction and hyalinization of the seminiferous tubules, leading to small, firm testes. Serum **inhibin levels are decreased** as a result of the Sertoli cell damage; Leydig cells are usually dysfunctional as well, resulting in **reduced testosterone** levels. The loss of feedback inhibition leads to **increased FSH and LH secretion**. Gynecomastia is caused by an increased ratio of estrogens to androgens (high gonadotropin levels increase aromatase activity, which increases conversion of testosterone to estradiol).

(Choice A) Hypogonadotropic (central) hypogonadism is caused by injury or dysfunction of the hypothalamus (eg, Kallmann syndrome) or pituitary gland (eg, adenomas). LH, FSH, and testosterone levels are all low, and spermatogenesis is impaired. Unlike in this patient, testes in central hypogonadism are atrophic and soft (not hyalinized and firm), and gynecomastia is uncommon because the decrease in gonadotropins reduces aromatase activity.

(Choice B) Azoospermia associated with a normal hormonal profile suggests an obstruction along the path from the testes to the seminal fluid (eg, congenital absence of the vas deferens in cystic fibrosis). In these patients, the testes and breasts are grossly normal.

(Choice C) Decreased LH, normal FSH, and elevated testosterone in the setting of a low sperm count suggest exogenous testosterone use. High androgen levels suppress LH secretion, decreasing endogenous testosterone production. Despite the high circulating levels of exogenous androgen, these patients have a low sperm count because local androgen concentrations in the seminiferous tubule are suboptimal for spermatogenesis. Over time, this leads to atrophy of the seminiferous tubules and soft, small testes.

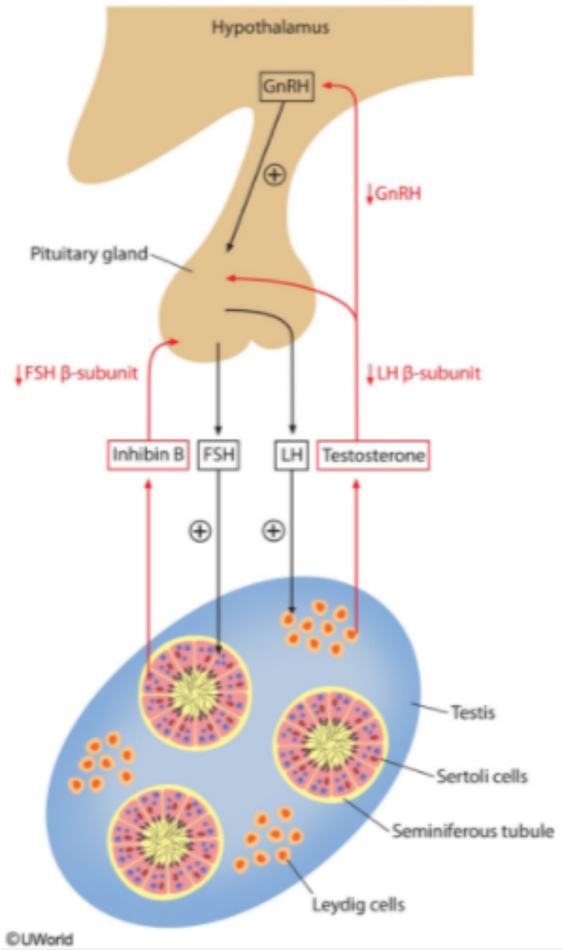
(Choice E) Normal LH and testosterone, elevated FSH, and a low sperm count can be seen in patients with cryptorchidism. In this condition, the seminiferous tubules are damaged (resulting in elevated FSH levels), and the interstitial Leydig cells are preserved (maintaining normal LH and testosterone levels).

Educational objective:
Klinefelter syndrome (47,XXY) causes infertility characterized by primary hypogonadism (elevated FSH and LH, low testosterone) and azoospermia. Other findings include long lower extremities; small, firm testes; and gynecomastia.

References

This patient has infertility, **gynecomastia**, and **long lower extremities**, findings which together are highly suggestive of **Klinefelter syndrome**.

Exhibit Display



Zoom In | Zoom Out | Reset | Add To New Card | Existing Card

References

(Choice A) Hypogonadotropic (central) hypogonadism is caused by injury or dysfunction of the hypothalamus (eg, Kallmann syndrome) or pituitary gland (eg, adenomas). LH, FSH, and testosterone levels are all low, and spermatogenesis is impaired. Unlike in this patient, testes in central hypogonadism are atrophic and soft (not hyalinized and firm), and gynecomastia is uncommon because the decrease in gonadotropins reduces aromatase activity.

(Choice B) Azoospermia associated with a normal hormonal profile suggests an obstruction along the path from the testes to the seminal fluid (eg, congenital absence of the vas deferens in cystic fibrosis). In these patients, the testes and breasts are grossly normal.

(Choice C) Decreased LH, normal FSH, and elevated testosterone in the setting of a low sperm count suggest exogenous testosterone use. High androgen levels suppress LH secretion, decreasing endogenous testosterone production. Despite the high circulating levels of exogenous androgen, these patients have a low sperm count because local androgen concentrations in the seminiferous tubule are suboptimal for spermatogenesis. Over time, this leads to atrophy of the seminiferous tubules and soft, small testes.

(Choice E) Normal LH and testosterone, elevated FSH, and a low sperm count can be seen in patients with cryptorchidism. In this condition, the seminiferous tubules are damaged (resulting in elevated FSH levels), and the interstitial Leydig cells are preserved (maintaining normal LH and testosterone levels).

Educational objective:
Klinefelter syndrome (47,XXY) causes infertility characterized by primary hypogonadism (elevated FSH and LH, low testosterone) and azoospermia. Other findings include long lower extremities; small, firm testes; and gynecomastia.

References

- Phenotypic differences in mosaic Klinefelter patients as compared with non-mosaic Klinefelter patients.
- Clinical review: Klinefelter syndrome--a clinical update.

Pathophysiology	Endocrine, Diabetes & Metabolism	Klinefelter syndrome
Subject	System	Topic

Copyright © UWorld. All rights reserved.

A 1-hour-old boy in the newborn nursery has jitteriness and irritability. His serum glucose is 21 mg/dL. The infant was born by cesarean delivery for macrosomia and failure to progress. The infant has not yet breastfed as his mother is still recovering from surgery. He weighs 4.5 kg (9 lb 15 oz). His mother was prescribed insulin for gestational diabetes but has not taken it regularly. She also has a history of depression and intravenous drug use. She denies use of illicit drugs during the pregnancy and tested negative for HIV and hepatitis B and C in her third trimester. Which of the following factors is the most likely cause of this neonate's hypoglycemia?

A. Beta cell hyperplasia

B. Glycogen storage disease

C. Hypothyroidism

D. Increased insulin-like growth factor 2 level

E. Placental transfer of insulin

Submit

A 1-hour-old boy in the newborn nursery has jitteriness and irritability. His serum glucose is 21 mg/dL. The infant was born by cesarean delivery for macrosomia and failure to progress. The infant has not yet breastfed as his mother is still recovering from surgery. He weighs 4.5 kg (9 lb 15 oz). His mother was prescribed insulin for gestational diabetes but has not taken it regularly. She also has a history of depression and intravenous drug use. She denies use of illicit drugs during the pregnancy and tested negative for HIV and hepatitis B and C in her third trimester. Which of the following factors is the most likely cause of this neonate's hypoglycemia?

- ✓ A. Beta cell hyperplasia (70%)
- B. Glycogen storage disease (2%)
- C. Hypothyroidism (2%)
- D. Increased insulin-like growth factor 2 level (8%)
- E. Placental transfer of insulin (16%)

Omitted
Correct answer
A

70%
Answered correctly

02 secs
Time Spent

01/25/2020
Last Updated

Explanation

Poor glucose control before or during pregnancy is associated with adverse effects on the fetus and newborn. **Macrosomia** (>4 kg [8 lb 14 oz]) is a common finding in infants of diabetic mothers. Poor maternal glucose control leads to excessive **transplacental glucose** transfer to the fetus, which stimulates fetal insulin production. Chronic stimulation of the fetal beta cells leads to **beta cell hyperplasia** and **hyperinsulinism**. Elevated insulin levels contribute to increased fat deposition and enhanced fetal growth, resulting in macrosomia.

10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40

Fetal effects of diabetes mellitus	
Embryopathy	• Congenital malformations* (eg, heart, neural tube defects)
Placental vasculopathy	• Asphyxia • Growth restriction • Polycythemia
Increased fetal insulin	• Macrosomia • Hypertrophic cardiomyopathy • Hypoglycemia after delivery

*Not common with gestational diabetes

©UWorld

Poor glucose control before or during pregnancy is associated with adverse effects on the fetus and newborn. **Macrosomia** (>4 kg [8 lb 14 oz]) is a common finding in infants of diabetic mothers. Poor maternal glucose control leads to excessive **transplacental glucose** transfer to the fetus, which stimulates fetal insulin production. Chronic stimulation of the fetal beta cells leads to **beta cell hyperplasia** and **hyperinsulinism**. Elevated insulin levels contribute to increased fat deposition and enhanced fetal growth, resulting in macrosomia.

After delivery, the infant experiences a sudden interruption in transplacental glucose transfer, but the hyperinsulinism remains due to the beta cell hyperplasia. This can result in rapid development of profound **hypoglycemia**, and affected infants require frequent feedings or parenteral glucose to prevent hypoglycemia and subsequent neurologic injury. In most cases, supportive care is all that is required; the beta cell hyperplasia will resolve over time.

(Choice B) Glycogen storage diseases are caused by enzymatic defects that impair glycogenolysis. Types that affect the liver typically present with hypoglycemia and lactic acidosis. Symptoms usually do not start until age 3-4 months, when glycogenolysis is needed to sustain blood glucose during longer feeding intervals.

Poor glucose control before or during pregnancy is associated with adverse effects on the fetus and newborn. **Macrosomia** (>4 kg [8 lb 14 oz]) is a common finding in infants of diabetic mothers. Poor maternal glucose control leads to excessive **transplacental glucose** transfer to the fetus, which stimulates fetal insulin production. Chronic stimulation of the fetal beta cells leads to **beta cell hyperplasia** and **hyperinsulinism**. Elevated insulin levels contribute to increased fat deposition and enhanced fetal growth, resulting in macrosomia.

After delivery, the infant experiences a sudden interruption in transplacental glucose transfer, but the hyperinsulinism remains due to the beta cell hyperplasia. This can result in rapid development of profound **hypoglycemia**, and affected infants require frequent feedings or parenteral glucose to prevent hypoglycemia and subsequent neurologic injury. In most cases, supportive care is all that is required; the beta cell hyperplasia will resolve over time.

(Choice B) Glycogen storage diseases are caused by enzymatic defects that impair glycogenolysis. Types that affect the liver typically present with hypoglycemia and lactic acidosis. Symptoms usually do not start until age 3-4 months, when glycogenolysis is needed to sustain blood glucose during longer feeding intervals.

(Choice C) Most infants with hypothyroidism are asymptomatic. Clinical manifestations include lethargy, irritability, and poor feeding and growth. Hypoglycemia shortly after delivery is not a common finding in neonatal hypothyroidism.

(Choice D) Insulin-like growth factor 2 (IGF-2) is important in fetal development. However, IGF levels are not increased in infants of diabetic mothers.

(Choice E) Maternal insulin is not transferred to the fetus but rather is catabolized by the placenta.

Educational objective:
Maternal hyperglycemia causes increased transplacental glucose delivery to the infant, fetal hyperglycemia, and, ultimately, beta cell hyperplasia. The resulting hyperinsulinemia caused by islet cell hyperplasia is associated with fetal macrosomia and hypoglycemia after delivery.

Pathophysiology	Endocrine, Diabetes & Metabolism	Gestational diabetes
Subject	System	Topic

Copyright © UWorld. All rights reserved.

A 43-year-old man comes to the emergency department due to painful muscle cramps. He also has had a tingling sensation around his mouth since earlier in the day and an intermittent sensation of choking in the throat. The patient reports a history of "high blood pressure and a thyroid disorder." On physical examination, he appears comfortable but anxious. Heart and lung sounds are normal. Light tapping anterior to the ear elicits twitching of the perioral muscles. Further discussion with this patient is most likely to reveal which of the following?

A. Excessive vitamin D intake

B. Frequent antacid use

C. New prescription for chlorthalidone

D. Nonadherence with levothyroxine

E. Recent thyroid surgery

Submit

A 43-year-old man comes to the emergency department due to painful muscle cramps. He also has had a tingling sensation around his mouth since earlier in the day and an intermittent sensation of choking in the throat. The patient reports a history of "high blood pressure and a thyroid disorder." On physical examination, he appears comfortable but anxious. Heart and lung sounds are normal. Light tapping anterior to the ear elicits twitching of the perioral muscles. Further discussion with this patient is most likely to reveal which of the following?

- A. Excessive vitamin D intake (7%)
- B. Frequent antacid use (4%)
- C. New prescription for chlorthalidone (6%)
- D. Nonadherence with levothyroxine (5%)
- ✓ E. Recent thyroid surgery (75%)

Omitted
Correct answer
E

75%
Answered correctly

01 sec
Time Spent

02/08/2020
Last Updated

Explanation

Hyperparathyroidism & hypoparathyroidism	
Hyperparathyroidism (↑ PTH)	**Hypoparathyroidism (↓ PTH)**
• ↑ Calcium, ↓ phosphate • Osteoporosis • Nephrolithiasis	• ↓ Calcium, ↑ phosphate • Tingling, numbness • Trousseau & Chvostek signs

Hyperparathyroidism & hypoparathyroidism	
Hyperparathyroidism (↑ PTH)	**Hypoparathyroidism (↓ PTH)**
• ↑ Calcium, ↓ phosphate • Osteoporosis • Nephrolithiasis • Polydipsia, polyuria • Constipation • Bone pain • Muscle pain	• ↓ Calcium, ↑ phosphate • Tingling, numbness • Trousseau & Chvostek signs • Muscle spasms • Seizures

This patient has symptoms of **hypocalcemia**, including muscle cramps, perioral paresthesias, and possible laryngospasm. Other manifestations of hypocalcemia may include Chvostek sign (facial muscle contraction elicited by tapping on the facial nerve anterior to the ear) and Trousseau sign (carpopedal spasm triggered by prolonged inflation of a blood pressure cuff around the arm). These signs of **neuromuscular hyperexcitability** become clinically apparent with serum calcium levels ≤7.0 mg/dL.

The most common cause of acute hypocalcemia is injury to the **parathyroid glands** during thyroid surgery due to direct trauma, devascularization, or inadvertent removal. Other causes of hypocalcemia include autoimmune hypoparathyroidism, sepsis, tumor lysis syndrome, acute pancreatitis, and severe vitamin D or magnesium deficiency.

(Choices A, B, and C) Excessive intake of vitamin D or calcium-containing antacids can cause hypercalcemia. Thiazide diuretics (eg, chlorthalidone) also can cause mild hypercalcemia due to increased calcium resorption in the distal and collecting tubule of the nephron. Typical presenting symptoms of hypercalcemia include constipation, polyuria/polydipsia, and muscle weakness.

(Choice D) Hyperthyroidism can cause hypercalcemia due to increased bone turnover. However, in hypothyroid states (eg, due to nonadherence to levothyroxine replacement) circulating calcium is usually normal. In general, hypothyroidism is characterized by chronic fatigue, weight gain, cold intolerance, and diminished reflexes.

Educational objective:

• Bone pain • Muscle pain	

This patient has symptoms of **hypocalcemia**, including muscle cramps, perioral paresthesias, and possible laryngospasm. Other manifestations of hypocalcemia may include Chvostek sign (facial muscle contraction elicited by tapping on the facial nerve anterior to the ear) and Trousseau sign (carpopedal spasm triggered by prolonged inflation of a blood pressure cuff around the arm). These signs of **neuromuscular hyperexcitability** become clinically apparent with serum calcium levels ≤7.0 mg/dL.

The most common cause of acute hypocalcemia is injury to the **parathyroid glands** during thyroid surgery due to direct trauma, devascularization, or inadvertent removal. Other causes of hypocalcemia include autoimmune hypoparathyroidism, sepsis, tumor lysis syndrome, acute pancreatitis, and severe vitamin D or magnesium deficiency.

(Choices A, B, and C) Excessive intake of vitamin D or calcium-containing antacids can cause hypercalcemia. Thiazide diuretics (eg, chlorthalidone) also can cause mild hypercalcemia due to increased calcium resorption in the distal and collecting tubule of the nephron. Typical presenting symptoms of hypercalcemia include constipation, polyuria/polydipsia, and muscle weakness.

(Choice D) Hyperthyroidism can cause hypercalcemia due to increased bone turnover. However, in hypothyroid states (eg, due to nonadherence to levothyroxine replacement) circulating calcium is usually normal. In general, hypothyroidism is characterized by chronic fatigue, weight gain, cold intolerance, and diminished reflexes.

Educational objective:
Hypocalcemia can cause muscle cramps, perioral paresthesias, hypotension, and neuromuscular hyperexcitability. Injury to the parathyroid glands during thyroid surgery is a common cause of hypoparathyroidism and acute hypocalcemia.

References

- Clinical and biochemical factors affecting postoperative hypocalcemia after near-total thyroidectomy.

Pathophysiology	Endocrine, Diabetes & Metabolism	Hypoparathyroidism
Subject	System	Topic

Copyright © UWorld. All rights reserved.

A 20-year-old woman comes to the emergency department with lethargy, abdominal pain, and nausea. She has had polyuria and excessive thirst for one day. She also complains of dysuria and chills over the last few days but did not seek medical care until today. Physical examination shows tachycardia and dry mucous membranes. Laboratory results are as follows:

Serum chemistry panel

Sodium	130 mEq/L
Chloride	93 mEq/L
Bicarbonate	12 mEq/L
Blood urea nitrogen	30 mg/dL
Creatinine	1.3 mg/dL
Calcium	10.0 mg/dL
Glucose	698 mg/dL

Which of the following electrolyte findings would most likely be seen in this patient?

	Extracellular potassium concentration	Intracellular potassium stores
A.	Decreased	Decreased
B.	Decreased	Increased
C.	Increased	Decreased
D.	Increased	Increased
E.	No Change	No change

Serum chemistry panel

Sodium	130 mEq/L
Chloride	93 mEq/L
Bicarbonate	12 mEq/L
Blood urea nitrogen	30 mg/dL
Creatinine	1.3 mg/dL
Calcium	10.0 mg/dL
Glucose	698 mg/dL

Which of the following electrolyte findings would most likely be seen in this patient?

	Extracellular potassium concentration	Intracellular potassium stores
A.	Decreased	Decreased
B.	Decreased	Increased
C.	Increased	Decreased
D.	Increased	Increased
E.	No Change	No change

Submit

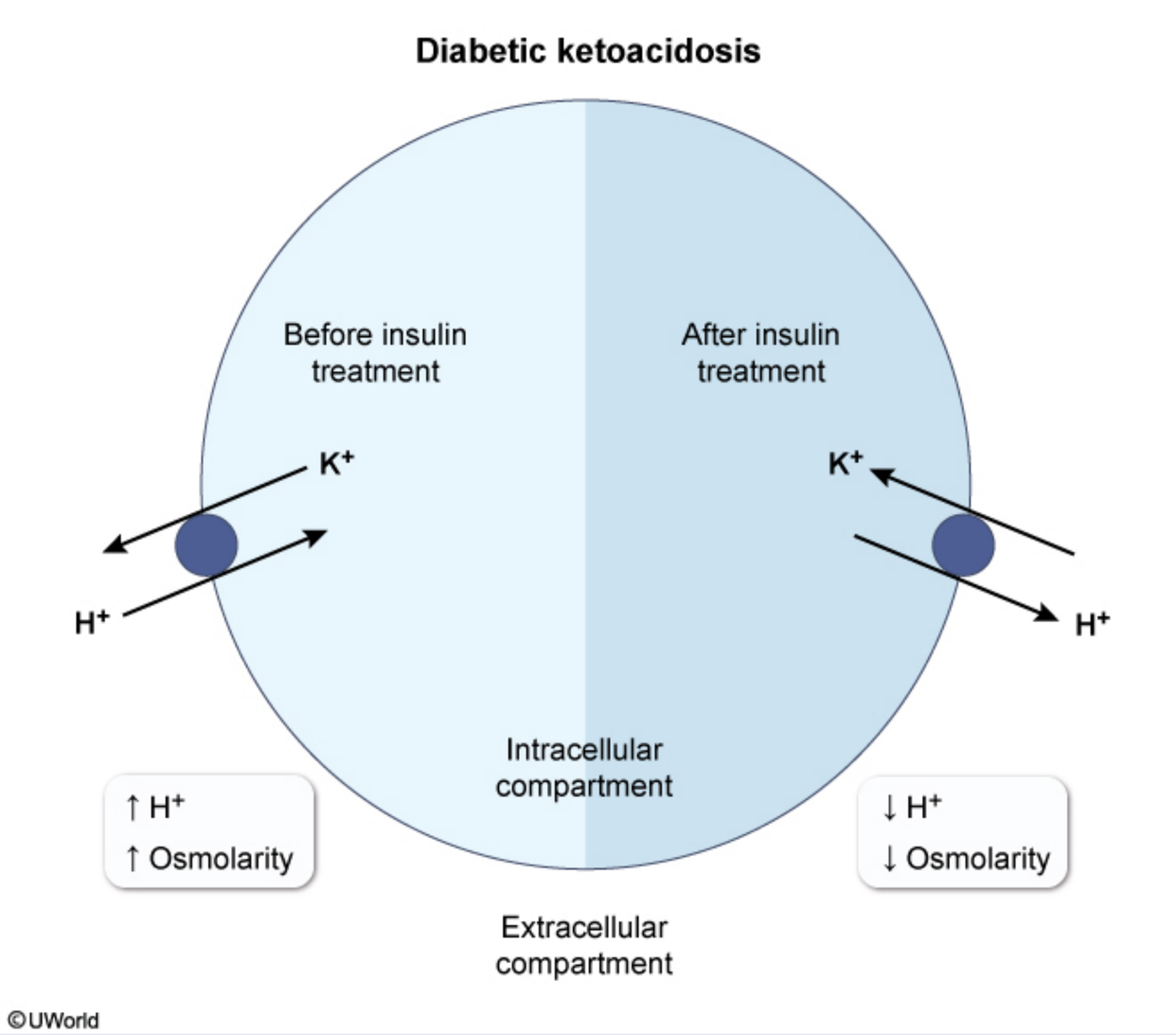
Serum chemistry panel

Sodium	130 mEq/L
Chloride	93 mEq/L
Bicarbonate	12 mEq/L
Blood urea nitrogen	30 mg/dL
Creatinine	1.3 mg/dL
Calcium	10.0 mg/dL
Glucose	698 mg/dL

Which of the following electrolyte findings would most likely be seen in this patient?

	Extracellular potassium concentration	Intracellular potassium stores
A.	Decreased (6%)	Decreased
B.	Decreased (12%)	Increased
✓ C.	Increased (77%)	Decreased
D.	Increased (2%)	Increased
E.	No Change (0%)	No change

10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40



This young patient has both clinical (eg, polyuria, polydipsia, volume depletion) and biochemical (eg, hyperglycemia, low bicarbonate, high anion

©UWorld

This young patient has both clinical (eg, polyuria, polydipsia, volume depletion) and biochemical (eg, hyperglycemia, low bicarbonate, high anion gap, decreased serum sodium levels) signs of diabetic ketoacidosis (DKA). DKA is often precipitated by infections, including urinary tract infections (likely in this patient). Patients with DKA lose significant amounts of potassium in the urine, primarily via glycosuria-induced osmotic diuresis and hypovolemia-mediated increase in aldosterone secretion. This results in a **total body potassium deficit** that is reflected by decreased intracellular potassium stores (since 98% of the body's potassium is stored intracellularly). Despite the low intracellular potassium levels, **extracellular potassium concentrations are normal or increased** due to the following mechanisms:

1. Loss of intracellular free water caused by increased plasma osmolality leads to extracellular movement of potassium secondary to increasing intracellular potassium concentration
2. Lack of insulin also causes extracellular shifting of potassium as insulin normally promotes cellular uptake of potassium

Clinicians must be careful when giving insulin and intravenous fluids during resuscitation of dehydrated, hyperglycemic patients. These interventions force potassium back into the cells, causing a precipitous drop in serum potassium due to the total body deficit. Despite normal or elevated serum potassium, timely administration of potassium supplementation is essential when treating a patient with DKA.

(Choice A) A decrease in both intra- and extracellular potassium levels is seen with mineralocorticoids excess, diuretic use, and chronic gastrointestinal losses.

(Choice B) Extracellular potassium concentration decreases following glucose and insulin administration as potassium moves into the intracellular compartment. Stimulation of beta-adrenergic receptors also causes increased transfer of potassium to the intracellular compartment.

(Choice D) Renal excretion of potassium is impaired in most patients with chronic renal failure, resulting in increased total body potassium storage and hyperkalemia.

(Choice E) Normal extracellular potassium levels are common in patients with DKA as the extracellular potassium shift is often mitigated by increased urinary potassium losses. However, intracellular potassium levels are always decreased in DKA.

Educational objective:
Most patients with diabetic ketoacidosis have normal to increased serum potassium levels despite a total body potassium deficit. Replacement of potassium is a crucial step in the management of patients with diabetic ketoacidosis.

decreased intracellular potassium stores (since 98% of the body's potassium is stored intracellularly). Despite the low intracellular potassium levels, **extracellular potassium concentrations are normal or increased** due to the following mechanisms:

1. Loss of intracellular free water caused by increased plasma osmolality leads to extracellular movement of potassium secondary to increasing intracellular potassium concentration
2. Lack of insulin also causes extracellular shifting of potassium as insulin normally promotes cellular uptake of potassium

Clinicians must be careful when giving insulin and intravenous fluids during resuscitation of dehydrated, hyperglycemic patients. These interventions force potassium back into the cells, causing a precipitous drop in serum potassium due to the total body deficit. Despite normal or elevated serum potassium, timely administration of potassium supplementation is essential when treating a patient with DKA.

(Choice A) A decrease in both intra- and extracellular potassium levels is seen with mineralocorticoids excess, diuretic use, and chronic gastrointestinal losses.

(Choice B) Extracellular potassium concentration decreases following glucose and insulin administration as potassium moves into the intracellular compartment. Stimulation of beta-adrenergic receptors also causes increased transfer of potassium to the intracellular compartment.

(Choice D) Renal excretion of potassium is impaired in most patients with chronic renal failure, resulting in increased total body potassium storage and hyperkalemia.

(Choice E) Normal extracellular potassium levels are common in patients with DKA as the extracellular potassium shift is often mitigated by increased urinary potassium losses. However, intracellular potassium levels are always decreased in DKA.

Educational objective:
Most patients with diabetic ketoacidosis have normal to increased serum potassium levels despite a total body potassium deficit. Replacement of potassium is a crucial step in the management of patients with diabetic ketoacidosis.

Pathophysiology	Endocrine, Diabetes & Metabolism	Diabetic ketoacidosis
Subject	System	Topic

Copyright © UWorld. All rights reserved.

A 45-year-old man comes to the emergency department after experiencing sudden-onset headache with brief loss of consciousness while working in his yard. CT scan of the brain reveals blood in the basal cistern from a ruptured intracranial aneurysm. The patient is hospitalized, and endovascular coiling of the aneurysm is performed. Over the next several days, his symptoms gradually improve but the patient develops worsening hyponatremia. Which of the following is the most likely cause of this patient's hyponatremia?

A. Defective central thirst regulation

B. Impaired renal concentrating ability

C. Inadequate dietary sodium intake

D. Increased antidiuretic hormone secretion

E. Stress-induced excessive cortisol levels

Submit

A 45-year-old man comes to the emergency department after experiencing sudden-onset headache with brief loss of consciousness while working in his yard. CT scan of the brain reveals blood in the basal cistern from a ruptured intracranial aneurysm. The patient is hospitalized, and endovascular coiling of the aneurysm is performed. Over the next several days, his symptoms gradually improve but the patient develops worsening hyponatremia. Which of the following is the most likely cause of this patient's hyponatremia?

- A. Defective central thirst regulation (19%)
- B. Impaired renal concentrating ability (9%)
- C. Inadequate dietary sodium intake (1%)
- ✓ D. Increased antidiuretic hormone secretion (63%)
- E. Stress-induced excessive cortisol levels (6%)

Omitted
Correct answer
D

63%
Answered correctly

04 secs
Time Spent

02/24/2020
Last Updated

Explanation

Syndrome of inappropriate antidiuretic hormone (SIADH)	
Pathophysiology	• Uncontrolled secretion of ADH • Leads to water retention & impaired urinary water excretion
	• CNS disturbances (stroke, hemorrhage, trauma) • Medications (eg, carbamazepine, SSRIs, NSAIDs)

Syndrome of inappropriate antidiuretic hormone (SIADH)	
Pathophysiology	• Uncontrolled secretion of ADH • Leads to water retention & impaired urinary water excretion
Causes	• CNS disturbances (stroke, hemorrhage, trauma) • Medications (eg, carbamazepine, SSRIs, NSAIDs) • Lung disease (eg, pneumonia) • Malignancy (eg, small-cell lung cancer)
Clinical findings	• Nausea, forgetfulness (mild hyponatremia) • Seizures, coma (severe hyponatremia) • Euvolemia (eg, moist mucous membranes, no edema, no JVD)
Laboratory findings	• Hyponatremia • Low serum osmolality • High urine osmolality • High urine sodium

ADH = antidiuretic hormone; **JVD** = jugular venous distension; **NSAIDs** = nonsteroidal anti-inflammatory drugs; **SSRIs** = selective serotonin reuptake inhibitors.

This patient likely has the **syndrome of inappropriate antidiuretic hormone secretion** (SIADH), the most common cause of **hyponatremia** following subarachnoid hemorrhage (SAH). Antidiuretic hormone (ADH) is normally released by the hypothalamus and posterior pituitary in response to elevated serum osmolality (eg, following water deprivation) or decreased arterial blood volume. ADH promotes renal water reabsorption, which leads to concentration of the urine, extracellular fluid volume expansion, and lowering of serum osmolality and serum sodium. Hypothalamic damage following SAH is thought to trigger **excessive production of ADH**, resulting in the classic SIADH features of **hypotonicity** (ie, low serum osmolarity), **hyponatremia**, and persistently concentrated urine (ie, **high urine osmolality**).

In addition to SIADH, hyponatremia after SAH can also be due to cerebral salt wasting (caused by increased secretion of brain natriuretic peptide,

inflammatory drugs; **SSRIs** = selective serotonin reuptake inhibitors.

This patient likely has the **syndrome of inappropriate antidiuretic hormone secretion** (SIADH), the most common cause of **hyponatremia** following subarachnoid hemorrhage (SAH). Antidiuretic hormone (ADH) is normally released by the hypothalamus and posterior pituitary in response to elevated serum osmolality (eg, following water deprivation) or decreased arterial blood volume. ADH promotes renal water reabsorption, which leads to concentration of the urine, extracellular fluid volume expansion, and lowering of serum osmolality and serum sodium. Hypothalamic damage following SAH is thought to trigger **excessive production of ADH**, resulting in the classic SIADH features of **hypotonicity** (ie, low serum osmolarity), **hyponatremia**, and persistently concentrated urine (ie, **high urine osmolality**).

In addition to SIADH, hyponatremia after SAH can also be due to cerebral salt wasting (caused by increased secretion of brain natriuretic peptide, which leads to urinary sodium losses) or acute cortisol deficiency (eg, from pituitary injury, leading to hypotension) **(Choice E)**. In both conditions, decreased extracellular fluid volume causes a secondary increase in ADH and worsening hyponatremia.

(Choice A) In primary polydipsia, defective central thirst regulation leads to excessive water intake and hyponatremia. ADH levels are low, rather than high. Primary polydipsia is typically seen with certain psychiatric conditions (eg, schizophrenia) or use of psychotropic medications. It is not commonly associated with SAH.

(Choice B) Impaired renal concentrating ability is seen in diabetes insipidus (DI), which occurs either due to ADH resistance (in nephrogenic DI) or decreased ADH production (in central DI). DI may follow cerebral injury; however, it does not cause hyponatremia. Rather, DI results in a clinical picture opposite that of SIADH, featuring hypernatremia, increased serum osmolality, and dilute urine (ie, low urine osmolality).

(Choice C) Inadequate dietary intake of sodium is a rare cause of hyponatremia primarily seen in cases of chronic alcohol abuse (eg, beer potomania). SIADH is a more likely cause of hyponatremia in this patient.

Educational objective:
Hyponatremia following cerebral injury (eg, subarachnoid hemorrhage) is commonly due to the syndrome of inappropriate antidiuretic hormone secretion. Injury to the hypothalamus leads to increased secretion of antidiuretic hormone, which in turn leads to water retention, low serum osmolality, and increased urinary sodium excretion.

References

- Diagnosis and management of subarachnoid hemorrhage.
- Hyponatremia after spontaneous aneurysmal subarachnoid hemorrhage – a prospective observational study.

(ie, low serum osmolarity), **hyponatremia**, and persistently concentrated urine (ie, **high urine osmolality**).

In addition to SIADH, hyponatremia after SAH can also be due to cerebral salt wasting (caused by increased secretion of brain natriuretic peptide, which leads to urinary sodium losses) or acute cortisol deficiency (eg, from pituitary injury, leading to hypotension) **(Choice E)**. In both conditions, decreased extracellular fluid volume causes a secondary increase in ADH and worsening hyponatremia.

(Choice A) In primary polydipsia, defective central thirst regulation leads to excessive water intake and hyponatremia. ADH levels are low, rather than high. Primary polydipsia is typically seen with certain psychiatric conditions (eg, schizophrenia) or use of psychotropic medications. It is not commonly associated with SAH.

(Choice B) Impaired renal concentrating ability is seen in diabetes insipidus (DI), which occurs either due to ADH resistance (in nephrogenic DI) or decreased ADH production (in central DI). DI may follow cerebral injury; however, it does not cause hyponatremia. Rather, DI results in a clinical picture opposite that of SIADH, featuring hypernatremia, increased serum osmolality, and dilute urine (ie, low urine osmolality).

(Choice C) Inadequate dietary intake of sodium is a rare cause of hyponatremia primarily seen in cases of chronic alcohol abuse (eg, beer potomania). SIADH is a more likely cause of hyponatremia in this patient.

Educational objective:
Hyponatremia following cerebral injury (eg, subarachnoid hemorrhage) is commonly due to the syndrome of inappropriate antidiuretic hormone secretion. Injury to the hypothalamus leads to increased secretion of antidiuretic hormone, which in turn leads to water retention, low serum osmolality, and increased urinary sodium excretion.

References

- Diagnosis and management of subarachnoid hemorrhage.
- Hyponatremia after spontaneous aneurysmal subarachnoid hemorrhage – a prospective observational study.

Pathophysiology	Endocrine, Diabetes & Metabolism	SIADH
Subject	System	Topic

Copyright © UWorld. All rights reserved.

A 20-year-old woman is brought to the emergency department due to intractable vomiting and abdominal pain. She has a several-week history of anorexia and weight loss. The patient has well-controlled primary hypothyroidism treated with levothyroxine but has not taken her medication for 2 days because of vomiting. Temperature is 37.6 C (99.7 F), blood pressure is 80/40 mm Hg, pulse is 120/min, and respirations are 18/min. On physical examination, she is mildly lethargic but oriented. Generalized hyperpigmentation is present and is most conspicuous over the face, neck, and dorsal surface of the hands. Urinalysis and chest x-ray are within normal limits. Finger-stick blood glucose is 60 mg/dL. A 1-L bolus of normal saline is rapidly infused, and high-flow intravenous fluids are continued. This patient also requires immediate treatment with which of the following medications?

A. Ceftriaxone
B. Dexamethasone
C. Dopamine
D. Epinephrine
E. Levothyroxine

Submit

A 20-year-old woman is brought to the emergency department due to intractable vomiting and abdominal pain. She has a several-week history of anorexia and weight loss. The patient has well-controlled primary hypothyroidism treated with levothyroxine but has not taken her medication for 2 days because of vomiting. Temperature is 37.6 C (99.7 F), blood pressure is 80/40 mm Hg, pulse is 120/min, and respirations are 18/min. On physical examination, she is mildly lethargic but oriented. Generalized hyperpigmentation is present and is most conspicuous over the face, neck, and dorsal surface of the hands. Urinalysis and chest x-ray are within normal limits. Finger-stick blood glucose is 60 mg/dL. A 1-L bolus of normal saline is rapidly infused, and high-flow intravenous fluids are continued. This patient also requires immediate treatment with which of the following medications?

A. Ceftriaxone (3%)
✓ B. Dexamethasone (56%)
C. Dopamine (4%)
D. Epinephrine (18%)
E. Levothyroxine (15%)

Omitted
Correct answer
B

56%
Answered correctly

01 sec
Time Spent

03/26/2020
Last Updated

Explanation

Acute adrenal insufficiency (adrenal crisis)	
	• Adrenal hemorrhage or infarction

Acute adrenal insufficiency (adrenal crisis)	
Etiology	• Adrenal hemorrhage or infarction • Illness/injury/surgery in patient with chronic AI • Pituitary apoplexy
Clinical features	• **Hypotension** & **shock** • Nausea, vomiting, abdominal pain • Fever, generalized weakness
Treatment	• **Hydrocortisone** or **dexamethasone** • Rapid intravenous volume repletion

AI = adrenal insufficiency.

This patient most likely has acute **adrenal crisis**. Her history of hypothyroidism puts her at increased risk for other autoimmune endocrinopathies (eg, autoimmune adrenalitis), and her weight loss and hyperpigmentation are suggestive of chronic **primary adrenal insufficiency** (Addison disease). In normal individuals, the adrenal glands respond to acute stress (eg, illness, surgery) with a compensatory increase in glucocorticoid production, but patients with adrenal insufficiency cannot mount such a response.

Adrenal crisis is characterized by **severe hypotension** and refractory shock. Associated symptoms include abdominal pain, vomiting, weakness, and fever. In addition to aggressive **fluid resuscitation**, treatment of adrenal crisis requires immediate **glucocorticoid supplementation** with hydrocortisone or dexamethasone. Treatment should begin immediately without waiting for results of diagnostic studies, and the response is usually rapid.

(Choice A) Antibiotics may be necessary if evidence of infection is found. However, treatment with glucocorticoids is warranted immediately, whereas the decision to start an antibiotic may be made when the presence of infection is more clearly established.

(Choices C and D) Dopamine is used in the treatment of shock and refractory cardiac failure. Epinephrine is used in the treatment of anaphylaxis, severe asthma, and cardiac arrest. However, hypotension in adrenal crisis is often refractory to vasopressors because glucocorticoids have a permissive effect on vasoconstriction.

disease). In normal individuals, the adrenal glands respond to acute stress (eg, illness, surgery) with a compensatory increase in glucocorticoid production, but patients with adrenal insufficiency cannot mount such a response.

Adrenal crisis is characterized by **severe hypotension** and refractory shock. Associated symptoms include abdominal pain, vomiting, weakness, and fever. In addition to aggressive **fluid resuscitation**, treatment of adrenal crisis requires immediate **glucocorticoid supplementation** with hydrocortisone or dexamethasone. Treatment should begin immediately without waiting for results of diagnostic studies, and the response is usually rapid.

(Choice A) Antibiotics may be necessary if evidence of infection is found. However, treatment with glucocorticoids is warranted immediately, whereas the decision to start an antibiotic may be made when the presence of infection is more clearly established.

(Choices C and D) Dopamine is used in the treatment of shock and refractory cardiac failure. Epinephrine is used in the treatment of anaphylaxis, severe asthma, and cardiac arrest. However, hypotension in adrenal crisis is often refractory to vasopressors because glucocorticoids have a permissive effect on vasoconstriction.

(Choice E) Clinical features of hypothyroid crisis may include hypoglycemia and hypotension, as seen in this patient, but would usually also include altered sensorium, hypothermia, bradycardia, and hypoventilation. In addition, due to the long plasma half life of levothyroxine, missing 2 days of therapy would be unlikely to cause a symptomatic drop in thyroid hormone levels.

Educational objective:
Patients with adrenal insufficiency are not able to increase glucocorticoid production in response to acute stress (eg, illness, surgery). Adrenal crisis is characterized by severe hypotension, abdominal pain, vomiting, weakness, and fever. In addition to aggressive fluid resuscitation, treatment requires immediate glucocorticoid supplementation.

References

- Extensive expertise in endocrinology. adrenal crisis.

Pathophysiology	Endocrine, Diabetes & Metabolism	Adrenal insufficiency
Subject	System	Topic

Copyright © UWorld. All rights reserved.

A 16-year-old girl comes to the office for a pre-participatory school sports examination. She plays on her high school soccer team and also frequently competes in local beauty pageants. The patient follows strict dietary limitations and exercises strenuously 2 hours a day. Onset of menses was at age 13, but her last menstrual period was 8 months ago. She otherwise feels well. Her height is 165 cm (5 ft 5 in) and her weight is 45.3 kg (100 lb), with a BMI of 16.6 kg/m^2. Physical examination shows a pale and thin girl with fine hair around her trunk, but the remainder is otherwise normal. Urine pregnancy test is negative. Which of the following is the most likely mechanism of her amenorrhea?

A. Hyperprolactinemia

B. Hyperthyroidism

C. Hypothalamic suppression

D. Primary ovarian failure

E. Primary pituitary dysfunction

Submit

A 16-year-old girl comes to the office for a pre-participatory school sports examination. She plays on her high school soccer team and also frequently competes in local beauty pageants. The patient follows strict dietary limitations and exercises strenuously 2 hours a day. Onset of menses was at age 13, but her last menstrual period was 8 months ago. She otherwise feels well. Her height is 165 cm (5 ft 5 in) and her weight is 45.3 kg (100 lb), with a BMI of 16.6 kg/m^2. Physical examination shows a pale and thin girl with fine hair around her trunk, but the remainder is otherwise normal. Urine pregnancy test is negative. Which of the following is the most likely mechanism of her amenorrhea?

- A. Hyperprolactinemia (3%)
- B. Hyperthyroidism (3%)
- ✓ C. Hypothalamic suppression (80%)
- D. Primary ovarian failure (7%)
- E. Primary pituitary dysfunction (6%)

Omitted
Correct answer
C

80%
Answered correctly

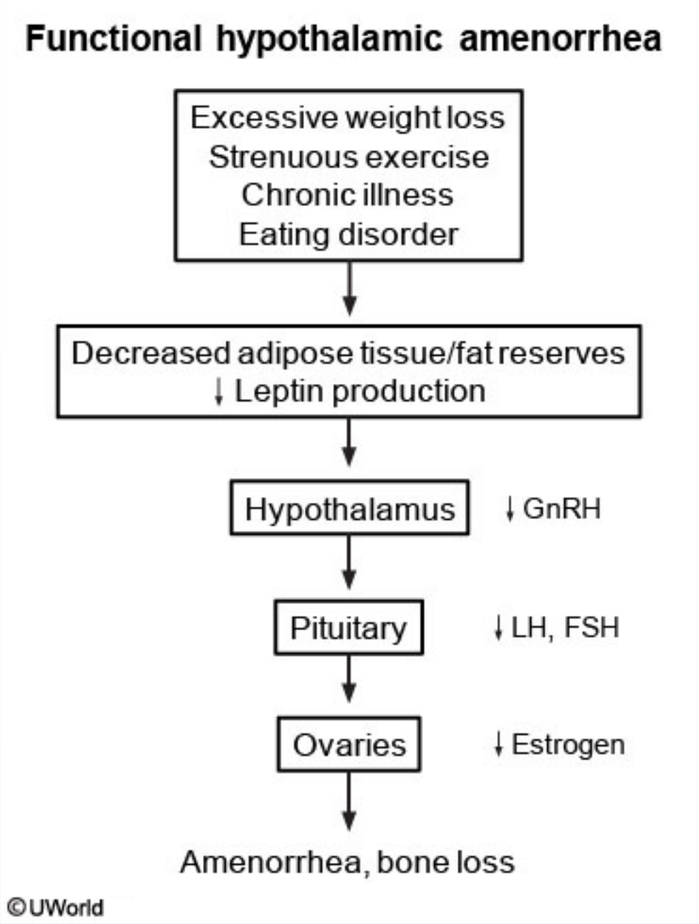
01 sec
Time Spent

01/20/2020
Last Updated

Explanation

Functional hypothalamic amenorrhea

Excessive weight loss
Strenuous exercise
Chronic illness



Amenorrhea can be categorized as primary (failure of menarche prior to age 15) or secondary (cessation of menstruation in premenopausal women who previously have had menses). Secondary amenorrhea can be due to hypothalamic, pituitary, ovarian, uterine, or other endocrine (eg, thyroid) disorders.

This patient has **secondary amenorrhea** associated with low body weight, frequent strenuous exercise, and lanugo (fine hair indicating inadequate caloric intake), suggesting **functional hypothalamic amenorrhea** (FHA). FHA is commonly seen in competitive athletes, dancers, fashion models, and others who maintain very low body weights. The underlying pathophysiology of FHA is incompletely understood but appears

Amenorrhea, bone loss

©UWorld

Amenorrhea can be categorized as primary (failure of menarche prior to age 15) or secondary (cessation of menstruation in premenopausal women who previously have had menses). Secondary amenorrhea can be due to hypothalamic, pituitary, ovarian, uterine, or other endocrine (eg, thyroid) disorders.

This patient has **secondary amenorrhea** associated with low body weight, frequent strenuous exercise, and lanugo (fine hair indicating inadequate caloric intake), suggesting **functional hypothalamic amenorrhea** (FHA). FHA is commonly seen in competitive athletes, dancers, fashion models, and others who maintain very low body weights. The underlying pathophysiology of FHA is incompletely understood but appears to involve reduced circulating **leptin** levels as a result of diminished adipose tissue stores. The decrease in leptin levels inhibits **pulsatile gonadotropin-releasing hormone (GnRH) release** from the hypothalamus, causing decreased pituitary LH and FSH secretion, low circulating estrogen levels, and amenorrhea.

(Choice A) Like FHA, hyperprolactinemia can cause secondary amenorrhea by suppressing normal GnRH release in the hypothalamus. Affected women may also develop galactorrhea. However, this patient's low body weight, caloric restriction, and strenuous exercise regimen are more consistent with FHA.

(Choice B) Hyperthyroidism can cause irregular menses or amenorrhea, along with weight loss. However, this patient has no other features to suggest a thyroid disorder (eg, goiter, temperature intolerance, diarrhea, hair loss).

(Choices D and E) The amenorrhea in patients with FHA stems from a deficiency in hypothalamic GnRH release, rather than a problem with the pituitary or ovaries; this patient has no other features of hypopituitarism.

Educational objective:
Functional hypothalamic amenorrhea results from loss of pulsatile gonadotropin-releasing hormone release from the hypothalamus and is caused by weight loss, strenuous exercise, systemic illness, or abnormal eating habits. Loss of cyclic gonadotropin release leads to a decrease in LH and FSH secretion from the pituitary, which in turn causes low circulating estrogen levels.

References

- Functional hypothalamic amenorrhea: current view on neuroendocrine aberrations.

A 34-year-old woman comes to the office with progressive weight gain over the past year. She also has weakness, easy bruising, and irregular menstrual periods. The patient takes no medications and has no drug allergies. Blood pressure is 150/90 mm Hg and pulse is 78/min. Laboratory studies reveal an elevated serum cortisol level that is not suppressed following administration of low-dose dexamethasone. Her 24-hour urine free-cortisol concentration and plasma ACTH are elevated. Which of the following histopathologic findings are most likely to be present in this patient's adrenal glands?

A. Adenoma of the zona glomerulosa

B. Atrophy of all layers of the adrenal cortex

C. Hyperplasia of the adrenal medulla

D. Hyperplasia of the zona fasciculata and reticularis

E. Neoplasia of adrenal medulla

Submit

A 34-year-old woman comes to the office with progressive weight gain over the past year. She also has weakness, easy bruising, and irregular menstrual periods. The patient takes no medications and has no drug allergies. Blood pressure is 150/90 mm Hg and pulse is 78/min. Laboratory studies reveal an elevated serum cortisol level that is not suppressed following administration of low-dose dexamethasone. Her 24-hour urine free-cortisol concentration and plasma ACTH are elevated. Which of the following histopathologic findings are most likely to be present in this patient's adrenal glands?

A. Adenoma of the zona glomerulosa (6%)

B. Atrophy of all layers of the adrenal cortex (8%)

C. Hyperplasia of the adrenal medulla (3%)

✓ D. Hyperplasia of the zona fasciculata and reticularis (80%)

E. Neoplasia of adrenal medulla (1%)

Omitted
Correct answer
D

80%
Answered correctly

01 sec
Time Spent

05/14/2020
Last Updated

Explanation

Common causes of Cushing syndrome		
	Etiology	Pathologic findings
ACTH	Cushing disease (ie, pituitary ACTH hypersecretion)	

Common causes of Cushing syndrome		
	Etiology	**Pathologic findings**
ACTH-dependent	Cushing disease (ie, pituitary ACTH hypersecretion)	• Bilateral hyperplasia involving the zona fasciculata & reticularis
	Ectopic ACTH syndrome (eg, paraneoplastic ACTH secretion)	
ACTH-independent	Adrenal adenoma or carcinoma	• Benign tumors are typically round, well-circumscribed lesions with cells similar to normal zona fasciculata • Malignant tumors are often irregular and poorly demarcated with considerable cellular pleomorphism • Atrophy of the zona fasciculata & reticularis in the uninvolved cortex regions

This patient has symptoms of hypercortisolism, including weight gain, weakness, and easy bruising. She also has increased 24-hour urine excretion of cortisol and an elevated serum cortisol level that is not suppressed by low-dose dexamethasone, which confirm the diagnosis of Cushing syndrome. In addition, her ACTH level is elevated (ACTH-dependent Cushing syndrome), which is most commonly due to an ACTH-secreting corticotroph pituitary adenoma (**Cushing disease**).

Initially, **excess ACTH** rapidly acts to increase adrenal blood flow and metabolic activity, primarily within the zona fasciculata and reticularis. ACTH stimulates the transfer of cholesterol to the inner mitochondrial membrane by steroidogenic acute regulatory protein (the rate limiting step in steroid production) and its conversion to pregnenolone by cholesterol side-chain cleavage enzyme. Increased pregnenolone availability results in **increased cortisol synthesis** within the zona fasciculata and **increased androgen production** within the zona reticularis (can lead to irregular menstruation, hirsutism). ACTH also has a trophic (growth) effect on the **zona fasciculata and reticularis**; as time passes, high levels of ACTH upregulate RNA and protein synthesis and induce cellular proliferation (**hyperplasia**).

(Choice A) Although increased ACTH can have a transient effect on aldosterone production, angiotensin II is the primary trophic hormone for the zona glomerulosa. Adenoma or nodular hyperplasia of the zona glomerulosa can be associated with increased secretion of mineralocorticoids

Cushing syndrome. In addition, her ACTH level is elevated (ACTH-dependent Cushing syndrome), which is most commonly due to an ACTH-secreting corticotroph pituitary adenoma (**Cushing disease**).

Initially, **excess ACTH** rapidly acts to increase adrenal blood flow and metabolic activity, primarily within the zona fasciculata and reticularis. ACTH stimulates the transfer of cholesterol to the inner mitochondrial membrane by steroidogenic acute regulatory protein (the rate limiting step in steroid production) and its conversion to pregnenolone by cholesterol side-chain cleavage enzyme. Increased pregnenolone availability results in **increased cortisol synthesis** within the zona fasciculata and **increased androgen production** within the zona reticularis (can lead to irregular menstruation, hirsutism). ACTH also has a trophic (growth) effect on the **zona fasciculata and reticularis**; as time passes, high levels of ACTH upregulate RNA and protein synthesis and induce cellular proliferation (**hyperplasia**).

(Choice A) Although increased ACTH can have a transient effect on aldosterone production, angiotensin II is the primary trophic hormone for the zona glomerulosa. Adenoma or nodular hyperplasia of the zona glomerulosa can be associated with increased secretion of mineralocorticoids (primary hyperaldosteronism [Conn syndrome]), which presents with hypertension and hypokalemia (muscle weakness).

(Choice B) Atrophy of the entire adrenal cortex is most commonly caused by autoimmune adrenalitis and presents with chronic adrenal insufficiency (Addison disease). There is a compensatory rise in ACTH secretion, but, unlike in this patient, urine cortisol excretion is not elevated.

(Choices C and E) Pheochromocytoma is a catecholamine-secreting tumor derived from the chromaffin cells of the adrenal medulla. Adrenal medullary hyperplasia is a rare disorder that may be a precursor to pheochromocytoma. These disorders typically present with symptoms of catecholamine excess (eg, palpitations, diaphoresis) and episodic hypertension. Patients have elevated blood and urine levels of catecholamines rather than cortisol.

Educational objective:
ACTH is the major trophic hormone of the zona fasciculata and reticularis, whereas the zona glomerulosa is primarily regulated by angiotensin II. Excess production of ACTH causes increased cortisol synthesis within the zona fasciculata (Cushing's manifestations) and increased androgen production within the zona reticularis (irregular menstruation, hirsutism in women).

Pathophysiology	Endocrine, Diabetes & Metabolism	Cushing syndrome
Subject	System	Topic

Copyright © UWorld. All rights reserved.

A 34-year-old man comes to the clinic due to frequent clumsiness. For the last 6 months, he has had repeated minor injuries from walking into doorways and stationary objects. The patient was also reprimanded at work for causing his supervisor to spill coffee when he bumped into her in the hallway. Medical history is notable for recurrent renal stones; following a subsequent diagnostic evaluation, the patient underwent definitive treatment with neck surgery 3 years ago. Family history is unavailable as the patient was adopted. Physical examination reveals bitemporal visual field defects. Cranial nerves, motor strength, and deep-tendon reflexes are otherwise normal. In addition to brain imaging, this patient should also be screened for which of the following tumors?

A. Adrenal
B. Bone
C. Breast
D. Colonic
E. Pancreatic

Submit

A 34-year-old man comes to the clinic due to frequent clumsiness. For the last 6 months, he has had repeated minor injuries from walking into doorways and stationary objects. The patient was also reprimanded at work for causing his supervisor to spill coffee when he bumped into her in the hallway. Medical history is notable for recurrent renal stones; following a subsequent diagnostic evaluation, the patient underwent definitive treatment with neck surgery 3 years ago. Family history is unavailable as the patient was adopted. Physical examination reveals bitemporal visual field defects. Cranial nerves, motor strength, and deep-tendon reflexes are otherwise normal. In addition to brain imaging, this patient should also be screened for which of the following tumors?

- A. Adrenal (24%)
- B. Bone (9%)
- C. Breast (2%)
- D. Colonic (2%)
- ✓ E. Pancreatic (60%)

Omitted
Correct answer
E

60%
Answered correctly

01 sec
Time Spent

06/25/2020
Last Updated

Explanation

Classification of multiple endocrine neoplasia	
Type 1	• **Primary hyperparathyroidism** (parathyroid adenomas or hyperplasia)

Classification of multiple endocrine neoplasia	
Type 1	• **Primary hyperparathyroidism** (parathyroid adenomas or hyperplasia) • Pituitary tumors (prolactin, visual defects) • Pancreatic tumors (especially gastrinomas)
Type 2A	• **Medullary thyroid cancer** (calcitonin) • Pheochromocytoma • Primary hyperparathyroidism (parathyroid hyperplasia)
Type 2B	• **Medullary thyroid cancer** (calcitonin) • Pheochromocytoma • Mucosal neuromas/marfanoid habitus

Multiple endocrine neoplasia type 1 (MEN1) is caused by mutations in the *MEN1* tumor suppressor gene and is characterized by tumors of the **p**arathyroid gland, **p**ituitary, and **p**ancreas (the "**3 Ps**"). Primary hyperparathyroidism is often the initial manifestation and usually presents with asymptomatic hypercalcemia or **renal stones**. Prolactin-secreting adenomas (prolactinomas) are the most common pituitary tumors. In premenopausal women, prolactinomas typically present with metabolic symptoms (eg, menstrual irregularities, galactorrhea); in men and postmenopausal women they usually present later when tumor enlargement leads to mass effect symptoms such as headache or **bitemporal visual field defects** (causing clumsiness in this patient) due to compression of the optic chiasm.

Entero-pancreatic neuroendocrine tumors are the third major tumor type in MEN1. Gastrinoma (leading to Zollinger-Ellison syndrome) is the most common, followed by insulinoma and nonfunctional tumors. These tumors are often metastatic and are a frequent cause of tumor-related death in MEN1. This patient has visual field defects consistent with a pituitary mass lesion, which warrants cerebral imaging. In addition, he has a history of symptomatic hyperparathyroidism. Given these features of MEN1, he is also at increased risk for entero-pancreatic neuroendocrine tumors.

(Choice A) Pheochromocytoma is an adrenal medullary tumor that occurs commonly in MEN2A and 2B. However, this patient's visual field

Multiple endocrine neoplasia type 1 (MEN1) is caused by mutations in the *MEN1* tumor suppressor gene and is characterized by tumors of the **p**arathyroid gland, **p**ituitary, and **p**ancreas (the "**3 Ps**"). Primary hyperparathyroidism is often the initial manifestation and usually presents with asymptomatic hypercalcemia or **renal stones**. Prolactin-secreting adenomas (prolactinomas) are the most common pituitary tumors. In premenopausal women, prolactinomas typically present with metabolic symptoms (eg, menstrual irregularities, galactorrhea); in men and postmenopausal women they usually present later when tumor enlargement leads to mass effect symptoms such as headache or **bitemporal visual field defects** (causing clumsiness in this patient) due to compression of the optic chiasm.

Entero-pancreatic neuroendocrine tumors are the third major tumor type in MEN1. Gastrinoma (leading to Zollinger-Ellison syndrome) is the most common, followed by insulinoma and nonfunctional tumors. These tumors are often metastatic and are a frequent cause of tumor-related death in MEN1. This patient has visual field defects consistent with a pituitary mass lesion, which warrants cerebral imaging. In addition, he has a history of symptomatic hyperparathyroidism. Given these features of MEN1, he is also at increased risk for entero-pancreatic neuroendocrine tumors.

(Choice A) Pheochromocytoma is an adrenal medullary tumor that occurs commonly in MEN2A and 2B. However, this patient's visual field defect suggests a pituitary tumor, which is more characteristic of MEN1 (not associated with pheochromocytoma).

(Choice B) Primary bone tumors are not increased in MEN1, although malignant neuroendocrine tumors may occasionally metastasize to bone.

(Choice C) The major inherited syndromes associated with breast cancer include *BRCA1* and *BRCA2* mutations (breast, ovarian, uterine/fallopian tube, pancreatic cancers). Less common syndromes include Cowden syndrome, Li-Fraumeni syndrome, and Peutz-Jeghers syndrome. Hyperparathyroidism and pituitary tumors are not prominent manifestations of any of these syndromes and are more consistent with MEN1.

(Choice D) Familial adenomatous polyposis is associated with an increased risk of colon cancer and with adrenal adenomas and thyroid cancer.

Educational objective:
Multiple endocrine neoplasia type 1 syndrome is characterized by tumors of the pituitary, parathyroid gland, and pancreas (the "3 Ps").

References

- Clinical practice guidelines for multiple endocrine neoplasia type 1 (MEN1).

A 45-year-old woman comes to the office due to a 4-month history of headaches and blurred vision. She takes no medications and has no other medical problems. After the initial laboratory workup, an abdominal CT is performed that shows a 2-cm left-sided adrenal mass. The patient undergoes an uncomplicated left-sided adrenalectomy. Gross examination of the adrenal gland demonstrates a well-defined yellowish tumor within the cortex. Assuming the tumor cells are functionally similar to cells from the outermost layer of the adrenal cortex, this patient would most likely have presented with which of the following additional symptoms?

A. Diarrhea and flushing

B. Excessive hair growth

C. Paresthesias and muscle weakness

D. Sweating and tremulousness

E. Weight gain and easy bruising

Submit

A 45-year-old woman comes to the office due to a 4-month history of headaches and blurred vision. She takes no medications and has no other medical problems. After the initial laboratory workup, an abdominal CT is performed that shows a 2-cm left-sided adrenal mass. The patient undergoes an uncomplicated left-sided adrenalectomy. Gross examination of the adrenal gland demonstrates a well-defined yellowish tumor within the cortex. Assuming the tumor cells are functionally similar to cells from the outermost layer of the adrenal cortex, this patient would most likely have presented with which of the following additional symptoms?

A. Diarrhea and flushing (6%)

B. Excessive hair growth (5%)

✓ C. Paresthesias and muscle weakness (58%)

D. Sweating and tremulousness (13%)

E. Weight gain and easy bruising (15%)

Omitted
Correct answer
C

58%
Answered correctly

01 sec
Time Spent

01/25/2020
Last Updated

Explanation

Primary hyperaldosteronism	
Etiology	• Bilateral adrenal hyperplasia (60%) • Unilateral adrenal adenoma

Explanation

Primary hyperaldosteronism	
Etiology	• Bilateral adrenal hyperplasia (60%) • Unilateral adrenal adenoma
Clinical features	• **Hypertension** • **Hypokalemic alkalosis**: Muscle weakness & paresthesias
Diagnosis	• **Elevated plasma aldosterone** • **Low plasma renin activity** • Aldosterone remains elevated following oral saline load

©UWorld

Presumably, this patient had symptoms of **primary hyperaldosteronism** due to an **aldosterone-producing adenoma** (Conn syndrome). Adrenocortical adenomas appear as well-defined yellowish tumors of the adrenal cortex on gross examination, regardless of functional status. This tumor is functionally similar to the outermost layer of the adrenal cortex, which normally produces aldosterone.

Aldosterone acts on renal cortical collecting ducts to facilitate the exchange of Na^+ for K^+ and H^+ in the tubular fluid. As a result, excess production of aldosterone causes renal Na^+ retention and excess urinary K^+ and H^+ secretion, resulting in hypertension, hypokalemia, and metabolic alkalosis. These electrolyte abnormalities can cause **paresthesias** and **muscle weakness** in some patients with primary hyperaldosteronism. Significant extracellular fluid volume expansion does not occur in primary hyperaldosteronism due to aldosterone escape.

(Choice A) Diarrhea and flushing may be seen in carcinoid syndrome, a rare condition most often caused by a serotonin (5-HT)-secreting tumor derived from neuroendocrine cells of the gastrointestinal tract.

(Choice B) Excessive hair growth (hirsutism) can result from excess androgen production. An adrenal tumor causing androgen hypersecretion

©UWorld

Presumably, this patient had symptoms of **primary hyperaldosteronism** due to an **aldosterone-producing adenoma** (Conn syndrome). Adrenocortical adenomas appear as well-defined yellowish tumors of the adrenal cortex on gross examination, regardless of functional status. This tumor is functionally similar to the outermost layer of the adrenal cortex, which normally produces aldosterone.

Aldosterone acts on renal cortical collecting ducts to facilitate the exchange of Na^+ for K^+ and H^+ in the tubular fluid. As a result, excess production of aldosterone causes renal Na^+ retention and excess urinary K^+ and H^+ secretion, resulting in hypertension, hypokalemia, and metabolic alkalosis. These electrolyte abnormalities can cause **paresthesias** and **muscle weakness** in some patients with primary hyperaldosteronism. Significant extracellular fluid volume expansion does not occur in primary hyperaldosteronism due to aldosterone escape.

(Choice A) Diarrhea and flushing may be seen in carcinoid syndrome, a rare condition most often caused by a serotonin (5-HT)-secreting tumor derived from neuroendocrine cells of the gastrointestinal tract.

(Choice B) Excessive hair growth (hirsutism) can result from excess androgen production. An adrenal tumor causing androgen hypersecretion would have the functionality of the third (innermost) layer of the adrenal cortex, the zona reticularis.

(Choice D) Sweating and tremulousness can be caused by excess circulating catecholamines, which may result from a pheochromocytoma. These tumors arise from the adrenal medulla rather than the adrenal cortex.

(Choice E) Patients with Cushing syndrome often develop weight gain due to central fat accumulation, along with easy bruising and weakening of the skin and subcutaneous connective tissue. Cortisol-secreting adrenal lesions would be functionally similar to the middle layer of the adrenal cortex (zona fasciculata).

Educational objective:
Hypersecreting adrenocortical tumors can have functionality resembling the outer (aldosterone/Conn syndrome), middle (cortisol/Cushing syndrome), or inner (androgens/hirsutism and virilization) layers of the adrenal cortex.

References

- Diagnosis and management of primary aldosteronism: an updated review.

Pathophysiology	Endocrine, Diabetes & Metabolism	Hyperaldosteronism
Subject	System	Topic

This tumor is functionally similar to the outermost layer of the adrenal cortex, which normally produces aldosterone.

Aldosterone acts on renal cortical collecting ducts to facilitate the exchange of Na^+ for K^+ and H^+ in the tubular fluid. As a result, excess production of aldosterone causes renal Na^+ retention and excess urinary K^+ and H^+ secretion, resulting in hypertension, hypokalemia, and metabolic alkalosis. These electrolyte abnormalities can cause **paresthesias** and **muscle weakness** in some patients with primary hyperaldosteronism. Significant extracellular fluid volume expansion does not occur in primary hyperaldosteronism due to aldosterone escape.

(Choice A) Diarrhea and flushing may be seen in carcinoid syndrome, a rare condition most often caused by a serotonin (5-HT)-secreting tumor derived from neuroendocrine cells of the gastrointestinal tract.

(Choice B) Excessive hair growth (hirsutism) can result from excess androgen production. An adrenal tumor causing androgen hypersecretion would have the functionality of the third (innermost) layer of the adrenal cortex, the zona reticularis.

(Choice D) Sweating and tremulousness can be caused by excess circulating catecholamines, which may result from a pheochromocytoma. These tumors arise from the adrenal medulla rather than the adrenal cortex.

(Choice E) Patients with Cushing syndrome often develop weight gain due to central fat accumulation, along with easy bruising and weakening of the skin and subcutaneous connective tissue. Cortisol-secreting adrenal lesions would be functionally similar to the middle layer of the adrenal cortex (zona fasciculata).

Educational objective:
Hypersecreting adrenocortical tumors can have functionality resembling the outer (aldosterone/Conn syndrome), middle (cortisol/Cushing syndrome), or inner (androgens/hirsutism and virilization) layers of the adrenal cortex.

References

- Diagnosis and management of primary aldosteronism: an updated review.

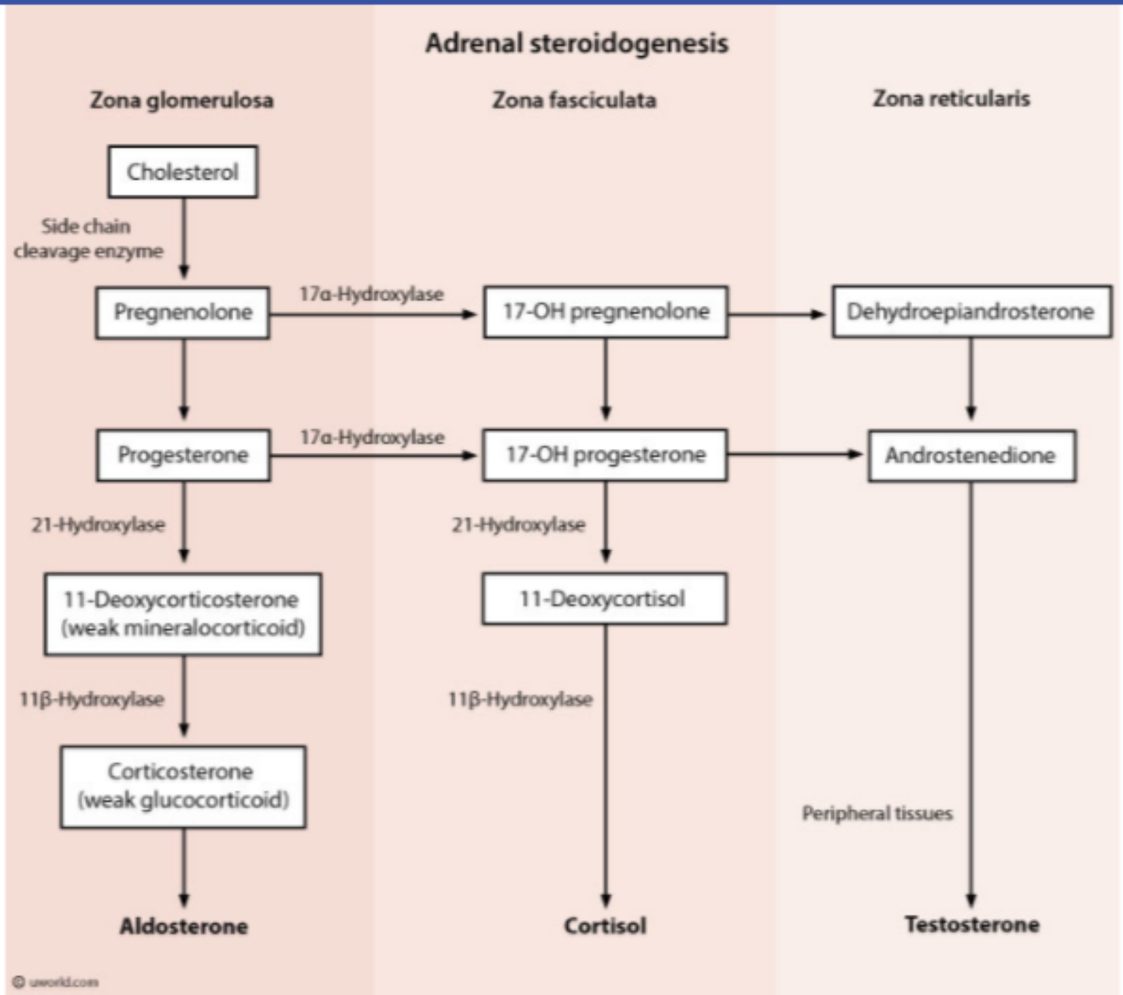
Pathophysiology	Endocrine, Diabetes & Metabolism	Hyperaldosteronism
Subject	System	Topic

Copyright © UWorld. All rights reserved.

Clinical

- Hypertension

Exhibit Display

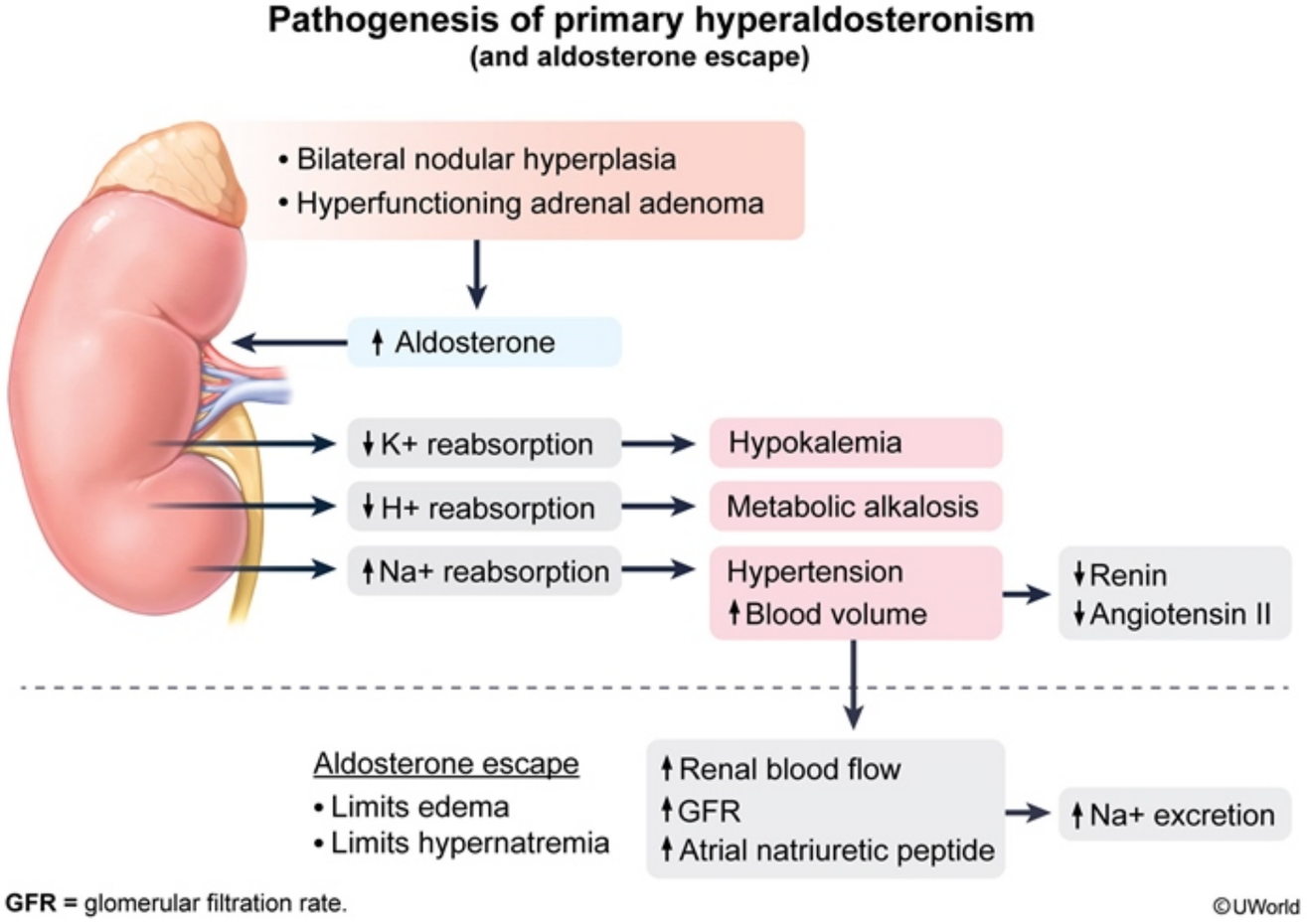


Zoom In | Zoom Out | Reset | Add To New Card | Existing Card

Educational objective:

Clinical
• Hypertension

Exhibit Display



Zoom In | Zoom Out | Reset | Add To New Card | Existing Card

Educational objective:

A 56-year-old woman comes to the office due to progressive weight gain and fatigue over the last 4 months. She also has had increasing difficulty in lifting heavy objects and climbing stairs. The patient has moderate, persistent bronchial asthma for which she uses inhaled corticosteroids and beta-2 agonists. Family history is significant for colon cancer in her father. Blood pressure is 160/90 mm Hg and pulse is 80/min. On physical examination, there is symmetric proximal muscle weakness of the upper and lower extremities. Fasting plasma glucose level is 135 mg/dL and 24-hour urinary cortisol is increased. Further evaluation reveals that high-dose, but not low-dose, dexamethasone suppresses serum cortisol levels. Serum ACTH levels are high-normal. Which of the following is the most likely cause of this patient's symptoms?

A. Adrenal adenoma
B. Adrenal carcinoma
C. Exogenous glucocorticoids
D. Pituitary adenoma
E. Small cell lung cancer

Submit

A 56-year-old woman comes to the office due to progressive weight gain and fatigue over the last 4 months. She also has had increasing difficulty in lifting heavy objects and climbing stairs. The patient has moderate, persistent bronchial asthma for which she uses inhaled corticosteroids and beta-2 agonists. Family history is significant for colon cancer in her father. Blood pressure is 160/90 mm Hg and pulse is 80/min. On physical examination, there is symmetric proximal muscle weakness of the upper and lower extremities. Fasting plasma glucose level is 135 mg/dL and 24-hour urinary cortisol is increased. Further evaluation reveals that high-dose, but not low-dose, dexamethasone suppresses serum cortisol levels. Serum ACTH levels are high-normal. Which of the following is the most likely cause of this patient's symptoms?

- A. Adrenal adenoma (9%)
- B. Adrenal carcinoma (1%)
- C. Exogenous glucocorticoids (9%)
- ✓ D. Pituitary adenoma (70%)
- E. Small cell lung cancer (9%)

Omitted
Correct answer
D

70%
Answered correctly

04 secs
Time Spent

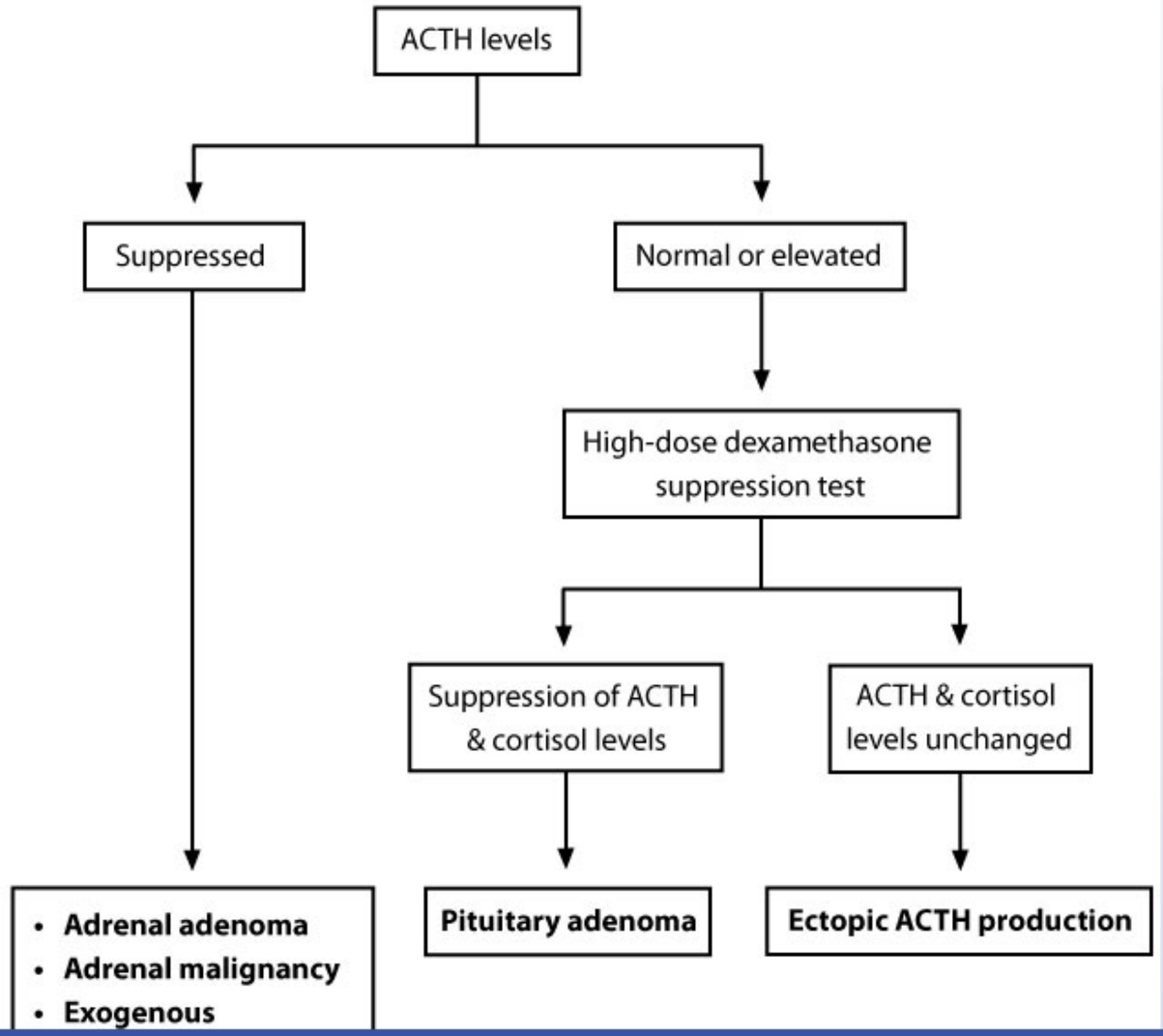
05/28/2020
Last Updated

Explanation

Diagnosing the cause of Cushing syndrome

ACTH levels

Diagnosing the cause of Cushing syndrome



©UWorld

This patient has weight gain, proximal muscle weakness, hypertension, and hyperglycemia, which are prominent features of Cushing syndrome. Screening tests for endogenous Cushing syndrome include **low-dose dexamethasone suppression testing**. In normal individuals, low doses of dexamethasone (a potent glucocorticoid) suppress ACTH and cortisol levels through negative feedback. However, in endogenous Cushing syndrome, ACTH and cortisol levels are not suppressed.

The most common causes of Cushing syndrome are shown in the flowchart and can be categorized on the basis of serum ACTH levels as either ACTH dependent (ACTH is high or inappropriately normal) or ACTH independent (ACTH is suppressed). In ACTH-dependent Cushing syndrome, if **high-dose dexamethasone suppresses ACTH** and cortisol secretion, a **pituitary source** of ACTH (ie, ACTH-secreting pituitary adenoma) is likely. In contrast, ectopic ACTH production (eg, from malignant tumors such as small cell lung cancer) is not suppressed by high-dose dexamethasone **(Choice E)**.

This patient has excessive cortisol production that is suppressed by high-dose but not low-dose dexamethasone. This is consistent with an ACTH-secreting corticotroph pituitary adenoma (**Cushing disease**), the most common cause of endogenous Cushing syndrome.

(Choices A and B) Excess cortisol production due to an autonomously functioning adrenal adenoma, adrenal carcinoma, or primary adrenocortical hyperplasia will cause Cushing syndrome with a suppressed ACTH level (ACTH independent). This patient's ACTH is elevated.

(Choice C) Administration of exogenous glucocorticoids is a common cause of Cushing syndrome. This is most common with systemic agents (eg, prednisone), but can occasionally be seen with topical or inhaled glucocorticoids. However, ACTH is suppressed in these cases.

Educational objective:
In Cushing syndrome due to an ACTH-secreting pituitary adenoma (Cushing disease), ACTH is high and cortisol production can be suppressed by high-dose, but not low-dose, dexamethasone. In patients with ectopic ACTH production (eg, from malignant tumors), cortisol and ACTH production are not suppressed by low- or high-dose dexamethasone.

References

- Cushing's disease.

Pathophysiology	Endocrine, Diabetes & Metabolism	Cushing syndrome
Subject	System	Topic

An infant is born at 39 weeks gestation to a 26-year-old woman. The delivery was uncomplicated, and Apgar scores were 8 and 9 at 1 and 5 minutes, respectively. The mother had gestational diabetes during pregnancy, which was controlled by diet alone. Physical examination of the infant shows clitoromegaly and partial fusion of the labioscrotal folds. Cytogenetic analysis reveals a 46,XX karyotype. Abdominal imaging shows bilateral adrenal hyperplasia. This patient is most likely deficient for an enzyme normally responsible for which of the following reactions?

A. Cholesterol → Pregnenolone

B. Dehydroepiandrosterone → Androstenedione

C. Progesterone → 11-deoxycorticosterone

D. Progesterone → 17-hydroxyprogesterone

E. Testosterone → Dihydrotestosterone

Submit

An infant is born at 39 weeks gestation to a 26-year-old woman. The delivery was uncomplicated, and Apgar scores were 8 and 9 at 1 and 5 minutes, respectively. The mother had gestational diabetes during pregnancy, which was controlled by diet alone. Physical examination of the infant shows clitoromegaly and partial fusion of the labioscrotal folds. Cytogenetic analysis reveals a 46,XX karyotype. Abdominal imaging shows bilateral adrenal hyperplasia. This patient is most likely deficient for an enzyme normally responsible for which of the following reactions?

- A. Cholesterol → Pregnenolone (2%)
- B. Dehydroepiandrosterone → Androstenedione (7%)
- ✓ C. Progesterone → 11-deoxycorticosterone (62%)
- D. Progesterone → 17-hydroxyprogesterone (24%)
- E. Testosterone → Dihydrotestosterone (3%)

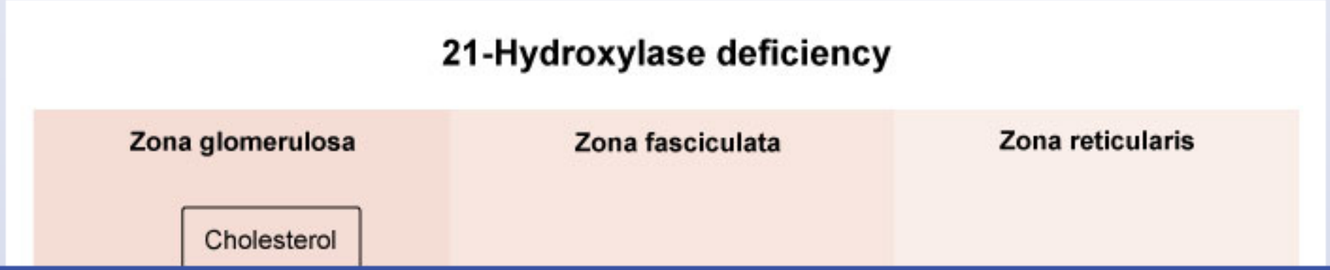
Omitted
Correct answer
C

62%
Answered correctly

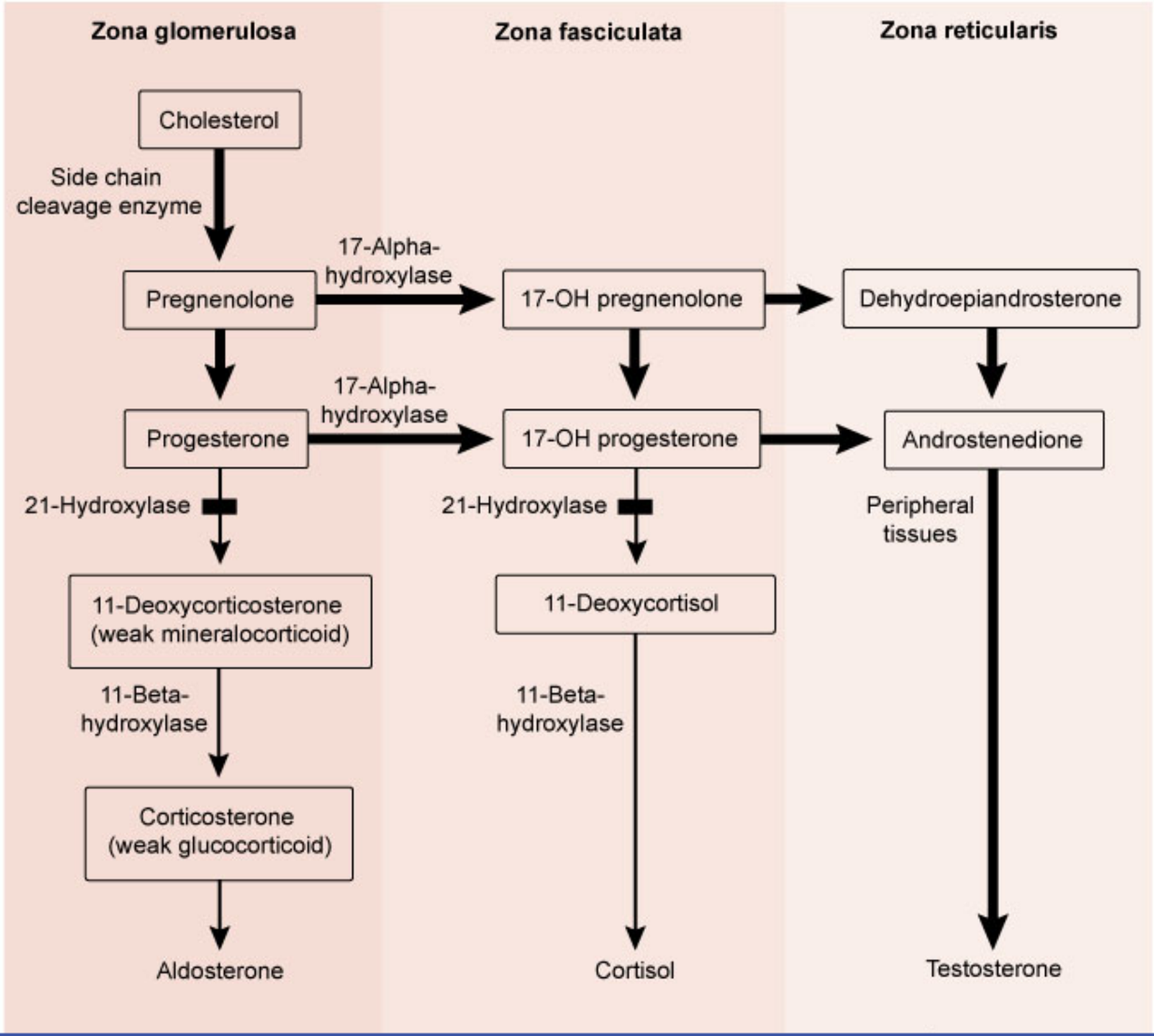
01 sec
Time Spent

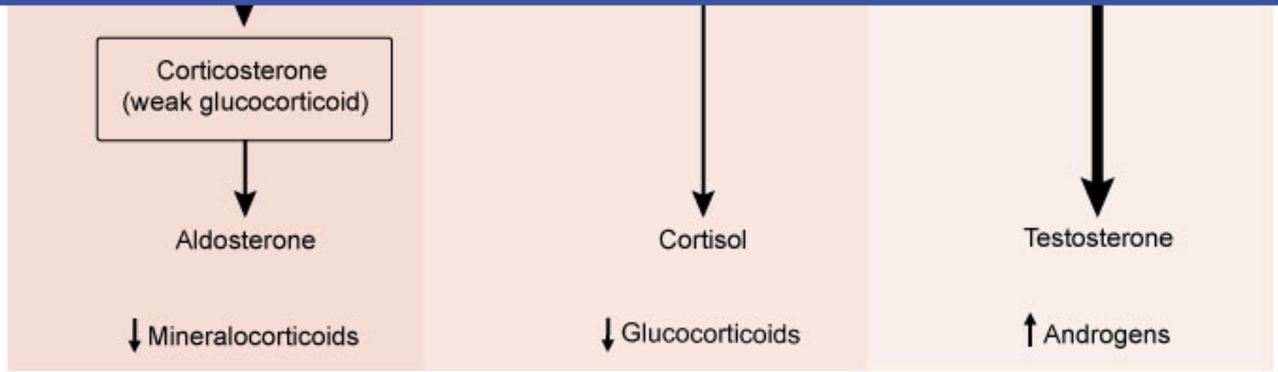
01/30/2020
Last Updated

Explanation



21-Hydroxylase deficiency





©UWorld

This patient's abdominal imaging and ambiguous genitalia are consistent with **congenital adrenal hyperplasia** (CAH). The most common cause of CAH is **21-hydroxylase deficiency**, accounting for 90% of all cases. This enzyme catalyzes the conversion of **progesterone to 11-deoxycorticosterone** (aldosterone precursor) in the zona glomerulosa, and 17-hydroxyprogesterone to 11-deoxycortisol (cortisol precursor) in the zona fasciculata.

In 21-hydroxylase deficiency, the adrenal gland cannot synthesize aldosterone and cortisol efficiently. ACTH levels increase as a result of low cortisol levels, stimulating **increased adrenal androgen** production by diverting the accumulating aldosterone and cortisol precursors toward the androgen biosynthetic pathway. Genetic females (46,XX) affected with classic 21-hydroxylase deficiency are usually identified at birth as increased androgen levels lead to ambiguous genitalia (**virilization**). However, genetic males (46,XY) have normal genitalia and therefore typically present later with symptoms of **salt-wasting** or precocious puberty.

Infants with 21-hydroxylase deficiency are often detected during routine newborn screening, and a high serum level of **17-hydroxyprogesterone** confirms the diagnosis.

(Choice A) Side-chain cleavage enzyme catalyzes the conversion of cholesterol into pregnenolone. Lack of this enzyme leads to absent steroid hormone synthesis. Complete enzyme deficiency is lethal due to absent placental progesterone synthesis.

(Choice B) Dehydroepiandrosterone is converted to androstenedione by 3β-hydroxysteroid dehydrogenase, an enzyme that also converts pregnenolone to progesterone and 17-hydroxypregnenolone to 17-hydroxyprogesterone. Although deficiency of this enzyme can result in adrenal insufficiency and ambiguous genitalia (in both sexes), it is a very rare cause of CAH.

deoxycorticosterone (aldosterone precursor) in the zona glomerulosa, and 17-hydroxyprogesterone to 11-deoxycortisol (cortisol precursor) in the zona fasciculata.

In 21-hydroxylase deficiency, the adrenal gland cannot synthesize aldosterone and cortisol efficiently. ACTH levels increase as a result of low cortisol levels, stimulating **increased adrenal androgen** production by diverting the accumulating aldosterone and cortisol precursors toward the androgen biosynthetic pathway. Genetic females (46,XX) affected with classic 21-hydroxylase deficiency are usually identified at birth as increased androgen levels lead to ambiguous genitalia (**virilization**). However, genetic males (46,XY) have normal genitalia and therefore typically present later with symptoms of **salt-wasting** or precocious puberty.

Infants with 21-hydroxylase deficiency are often detected during routine newborn screening, and a high serum level of **17-hydroxyprogesterone** confirms the diagnosis.

(Choice A) Side-chain cleavage enzyme catalyzes the conversion of cholesterol into pregnenolone. Lack of this enzyme leads to absent steroid hormone synthesis. Complete enzyme deficiency is lethal due to absent placental progesterone synthesis.

(Choice B) Dehydroepiandrosterone is converted to androstenedione by 3β-hydroxysteroid dehydrogenase, an enzyme that also converts pregnenolone to progesterone and 17-hydroxypregnenolone to 17-hydroxyprogesterone. Although deficiency of this enzyme can result in adrenal insufficiency and ambiguous genitalia (in both sexes), it is a very rare cause of CAH.

(Choice D) Synthesis of 17-hydroxyprogesterone from progesterone is catalyzed by 17α-hydroxylase. Deficiency of this enzyme causes mineralocorticoid excess and impaired androgen synthesis. Genetic males have ambiguous genitalia, whereas genetic females appear phenotypically normal.

(Choice E) 5α-reductase deficiency prevents the conversion of testosterone to dihydrotestosterone, the hormone responsible for the development of male external genitalia. Affected genetic males, not females, are born with ambiguous genitalia.

Educational objective:
The most common form of congenital adrenal hyperplasia is 21-hydroxylase deficiency. Genetically female infants typically have ambiguous genitalia (virilization) at birth, whereas males have phenotypically normal genitalia, with salt-wasting or precocious puberty appearing later. Elevated 17-hydroxyprogesterone is diagnostic.

References

- Congenital adrenal hyperplasia

deoxycorticosterone (aldosterone precursor) in the zona glomerulosa, and 17-hydroxyprogesterone to 11-deoxycortisol (cortisol precursor) in the

Exhibit Display

Clinical phenotypes of 21-hydroxylase deficiency			
	Classic, salt-wasting	Classic, non-salt-wasting	Non-classic, delayed
Degree of 21-hydroxylase deficiency	Severe	Moderate	Mild
Clinical presentation	Girls present at birth with ambiguous genitalia Boys present at 1-2 weeks with failure to thrive, dehydration, hyperkalemia & hyponatremia	Girls present at birth with ambiguous genitalia Boys present at 2-4 years with signs of early virilization	Premature pubarche or sexual precocity in school-age children Young women can present with acne, hirsutism & menstrual irregularity

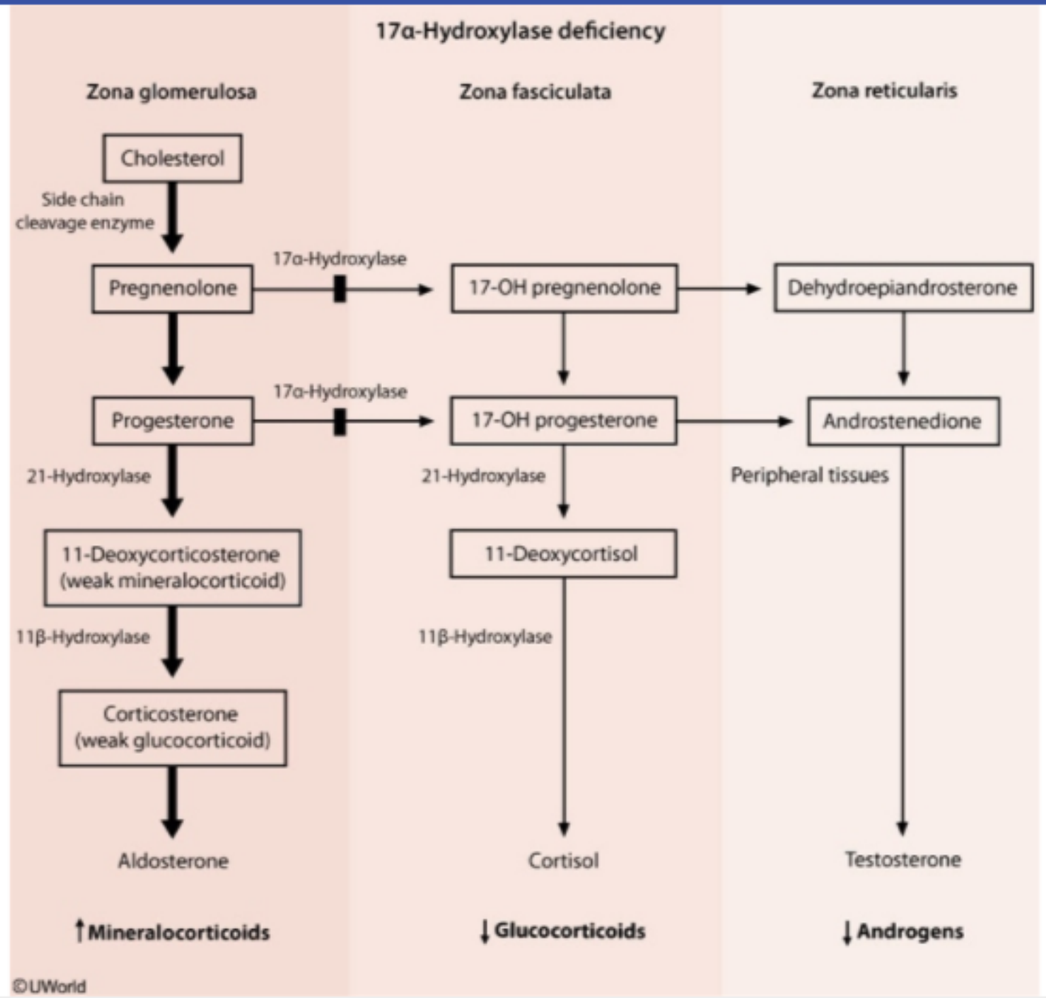
©UWorld

Zoom In | Zoom Out | Reset | Add To New Card | Existing Card

- Congenital adrenal hyperplasia

deoxycorticosterone (aldosterone precursor) in the zona glomerulosa, and 17-hydroxyprogesterone to 11-deoxycortisol (cortisol precursor) in the

Exhibit Display

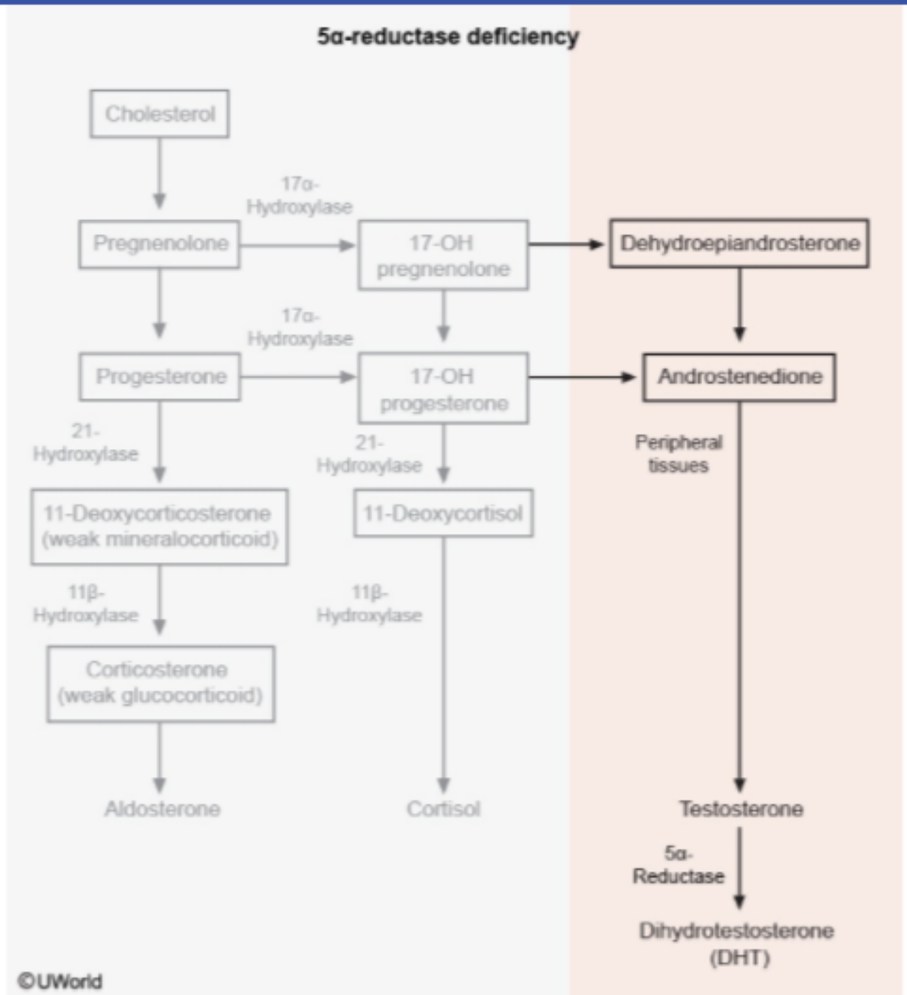


Zoom In Zoom Out Reset Add To New Card | Existing Card

- Congenital adrenal hyperplasia

deoxycorticosterone (aldosterone precursor) in the zona glomerulosa, and 17-hydroxyprogesterone to 11-deoxycortisol (cortisol precursor) in the

Exhibit Display



Zoom In | Zoom Out | Reset | Add To New Card | Existing Card

- Congenital adrenal hyperplasia

A 34-year-old, previously healthy woman comes to the office due to irregular menstruation and a 4.5 kg (10-lb) weight gain over the past 6 months. The patient also reports muscle weakness causing difficulty climbing stairs or lifting her child. Blood pressure is 152/86 mm Hg and pulse is 72/min. BMI is 31 kg/m^2. Physical examination shows excessive fat accumulation in the abdomen and supraclavicular area. Sun-exposed areas and skin creases are hyperpigmented and there are wide striae over the abdomen. Coarse hair is present on the face, chest, and abdomen. Which of the following sets of laboratory findings are most likely to be seen in this patient?

	24-hour urinary cortisol	Serum ACTH	Serum DHEAS
A.	↑	↑	↑
B.	↓	↑	↓
C.	↑	↓	↓
D.	Normal	Normal	↑
E.	↓	↓	↓

Submit

A 34-year-old, previously healthy woman comes to the office due to irregular menstruation and a 4.5 kg (10-lb) weight gain over the past 6 months. The patient also reports muscle weakness causing difficulty climbing stairs or lifting her child. Blood pressure is 152/86 mm Hg and pulse is 72/min. BMI is 31 kg/m^2. Physical examination shows excessive fat accumulation in the abdomen and supraclavicular area. Sun-exposed areas and skin creases are hyperpigmented and there are wide striae over the abdomen. Coarse hair is present on the face, chest, and abdomen. Which of the following sets of laboratory findings are most likely to be seen in this patient?

	24-hour urinary cortisol	Serum ACTH	Serum DHEAS
✓ A. (79%)	↑	↑	↑
B. (3%)	↓	↑	↓
C. (14%)	↑	↓	↓
D. (1%)	Normal	Normal	↑
E. (0%)	↓	↓	↓

Omitted
Correct answer
A

79%
Answered correctly

02 secs
Time Spent

02/29/2020
Last Updated

Explanation

Categorization of Cushing syndrome		
	Etiology	**Distinguishing findings**
ACTH-dependent	• Cushing disease (ACTH-secreting pituitary adenoma) • Ectopic ACTH secretion	• Hyperpigmentation • Hyperandrogenism (eg, hirsutism, oligo/amenorrhea) • ↑ ACTH
ACTH-independent	• Adrenal mass (adenoma or carcinoma) • Exogenous glucocorticoids	• ↓ ACTH

This patient with central obesity, proximal muscle weakness, striae, and hypertension has common features of cortisol excess (ie, Cushing syndrome). Other possible findings include hyperglycemia, dermal atrophy, and easy bruisability. Hypercortisolism can be confirmed on finding an elevated late-night salivary cortisol concentration or **increased 24-hour urine cortisol** excretion.

Cushing syndrome can be categorized as ACTH-dependent (ie, ↑**ACTH** stimulating excess cortisol production) or ACTH-independent (ie, glucocorticoid excess not caused by ACTH). Excess ACTH secretion causes identifiable clinical findings:

- **Hyperpigmentation:** Both ACTH and alpha-melanocyte-stimulating hormone (MSH) are derived from pro-opiomelanocortin, leading to cosecretion of alpha-MSH. ACTH also directly stimulates the MC2R receptor on melanocytes.
- Androgenization: ACTH stimulates production of adrenal androgens (eg, ↑**DHEAS** [dehydroepiandrosterone sulfate], androstenedione). This leads to **hirsutism**, **menstrual abnormalities**, and oily skin.

This patient's hyperpigmentation and hirsutism are consistent with ACTH-dependent hypercortisolism, likely due to a corticotroph pituitary adenoma (**Cushing disease**).

(Choice B) Primary adrenal insufficiency leads to decreased cortisol levels (and decreased urinary cortisol excretion) with a compensatory rise in ACTH. Hyperpigmentation may be present, but adrenal androgen production is often diminished (due to loss of androgen-producing adrenocortical cells) and hirsutism is not present.

(Choices C and E) ACTH-independent Cushing syndrome due to a cortisol-producing adrenal adenoma is characterized by increased urinary

- Androgenization: ACTH stimulates production of adrenal androgens (eg, ↑**DHEAS** [dehydroepiandrosterone sulfate], androstenedione). This leads to **hirsutism**, **menstrual abnormalities**, and oily skin.

This patient's hyperpigmentation and hirsutism are consistent with ACTH-dependent hypercortisolism, likely due to a corticotroph pituitary adenoma (**Cushing disease**).

(Choice B) Primary adrenal insufficiency leads to decreased cortisol levels (and decreased urinary cortisol excretion) with a compensatory rise in ACTH. Hyperpigmentation may be present, but adrenal androgen production is often diminished (due to loss of androgen-producing adrenocortical cells) and hirsutism is not present.

(Choices C and E) ACTH-independent Cushing syndrome due to a cortisol-producing adrenal adenoma is characterized by increased urinary cortisol excretion with suppressed ACTH levels. Exogenous glucocorticoids also cause suppression of ACTH, but with decreased production (and urinary excretion) of cortisol. Low cortisol excretion and ACTH levels are also seen in central adrenal insufficiency. Because ACTH is low in these states, patients do not have hyperpigmentation or hyperandrogenic features (eg, hirsutism).

(Choice D) Polycystic ovary syndrome is characterized by excessive ovarian production of androgens. Common clinical features include oligo/amenorrhea, obesity, and hirsutism. However, ACTH and cortisol production are unaffected, and hyperpigmentation is not seen.

Educational objective:
Cushing syndrome can be categorized as ACTH-dependent or ACTH-independent. Excess ACTH secretion in ACTH-dependent Cushing syndrome leads to hyperpigmentation. In addition to increased cortisol production, ACTH stimulates production of adrenal androgens (eg, testosterone, dehydroepiandrosterone sulfate) leading to hirsutism and menstrual irregularities.

References

- Cushing's disease.

Pathophysiology	Endocrine, Diabetes & Metabolism	Cushing syndrome
Subject	System	Topic

Copyright © UWorld. All rights reserved.

A 23-year-old man is brought to the emergency department by his roommate due to progressive weakness and confusion. The roommate says that the patient has been "drinking water all of the time and using the bathroom constantly" since he got sick with a cold 2 days ago. Temperature is 37.8 C (100 F), blood pressure is 96/58 mm Hg, and pulse is 112/min. Physical examination shows dry mucous membranes and his urine has a strong, fruity odor. Laboratory results are as follows:

Serum chemistry

Sodium	134 mEq/L
Potassium	3.8 mEq/L
Chloride	100 mEq/L
Bicarbonate	14 mEq/L
Creatinine	1.0 mg/dL
Glucose	498 mg/dL
pH	7.17
$PaCO_2$	40 mm Hg

Based on the current laboratory findings, which of the following is most likely occurring in this patient?

A. Adrenal insufficiency
B. Increased renal bicarbonate loss
C. Low plasma renin activity
D. Renal tubular necrosis
E. Respiratory failure

Serum chemistry

Sodium	134 mEq/L
Potassium	3.8 mEq/L
Chloride	100 mEq/L
Bicarbonate	14 mEq/L
Creatinine	1.0 mg/dL
Glucose	498 mg/dL
pH	7.17
$PaCO_2$	40 mm Hg

Based on the current laboratory findings, which of the following is most likely occurring in this patient?

A. Adrenal insufficiency
B. Increased renal bicarbonate loss
C. Low plasma renin activity
D. Renal tubular necrosis
E. Respiratory failure

Submit

Serum chemistry

Sodium	134 mEq/L
Potassium	3.8 mEq/L
Chloride	100 mEq/L
Bicarbonate	14 mEq/L
Creatinine	1.0 mg/dL
Glucose	498 mg/dL
pH	7.17
$PaCO_2$	40 mm Hg

Based on the current laboratory findings, which of the following is most likely occurring in this patient?

A. Adrenal insufficiency (9%)

B. Increased renal bicarbonate loss (49%)

C. Low plasma renin activity (5%)

D. Renal tubular necrosis (9%)

✓ E. Respiratory failure (25%)

Omitted
Correct answer

25%
Answered correctly

05 secs
Time Spent

04/05/2020
Last Updated

Appropriate compensatory $PaCO_2$ or bicarbonate changes in acid-base disorders	
Metabolic acidosis (acute or chronic)	Expected $PaCO_2$ = (1.5 × bicarbonate) + 8 ± 2 (Winters formula)
Metabolic alkalosis (acute or chronic)	~7 mm Hg ↑ in $PaCO_2$ per 10 mEq/L ↑ in bicarbonate
Respiratory acidosis (chronic only*)	~4 mEq/L ↑ in bicarbonate per 10 mm Hg ↑ in $PaCO_2$
Respiratory alkalosis (chronic only*)	~4 mEq/L ↓ in bicarbonate per 10 mm Hg ↓ in $PaCO_2$

*Compensation for respiratory disturbances is minimal in the acute setting. The full level of chronic compensation is achieved after ~72 hr. For simplicity, normal baseline $PaCO_2$ and bicarbonate should be considered 40 mm Hg and 24 mEq/L, respectively.

The combination of acute-onset polyuria, polydipsia, volume depletion, and a fruity odor to the urine or breath is suggestive of **diabetic ketoacidosis**, which in this patient was most likely precipitated by a viral infection. The laboratory findings of **hyperglycemia** and anion gap metabolic acidosis confirm the diagnosis. The high anion gap is due to the presence of unmeasured anionic ketoacids (eg, beta-hydroxybutyrate, acetoacetate).

Patients with metabolic acidosis usually develop a **compensatory respiratory alkalosis** by hyperventilating (eg, Kussmaul respirations), which helps mitigate the acidemia by causing a drop in the $PaCO_2$. However, if the $PaCO_2$ persists above the expected compensatory range (given by Winter formula, where $PaCO_2 = [1.5 * HCO_3^-] + 8 \pm 2$), it indicates a superimposed respiratory acidosis that is interfering with normal respiratory compensation.

This patient's serum HCO_3^- of 14 mEq/L should be compensated by a $PaCO_2$ in the range of 27-31 mm Hg. However, his **$PaCO_2$ is higher than expected**, indicating that he has a mixed acid-base disturbance consisting of metabolic and respiratory acidoses. Severe diabetic ketoacidosis can cause pulmonary edema, respiratory fatigue, and decreased mental status, which may lead to hypoventilation and subsequent hypercarbic respiratory failure.

helps mitigate the acidemia by causing a drop in the $PaCO_2$. However, if the $PaCO_2$ persists above the expected compensatory range (given by Winter formula, where $PaCO_2 = [1.5 * HCO_3^-] + 8 \pm 2$), it indicates a superimposed respiratory acidosis that is interfering with normal respiratory compensation.

This patient's serum HCO_3^- of 14 mEq/L should be compensated by a $PaCO_2$ in the range of 27-31 mm Hg. However, his **$PaCO_2$ is higher than expected**, indicating that he has a mixed acid-base disturbance consisting of metabolic and respiratory acidoses. Severe diabetic ketoacidosis can cause pulmonary edema, respiratory fatigue, and decreased mental status, which may lead to hypoventilation and subsequent hypercarbic **respiratory failure**.

(Choice A) Acute adrenal insufficiency is characterized by mineralocorticoid deficiency, which can result in hypotension, hyperkalemia, and mild hyperchloremic acidosis. This patient's laboratory findings are not consistent with acute adrenal insufficiency.

(Choice B) Ketoacidosis results in a low serum pH that causes much of the serum bicarbonate (HCO_3^-) to be converted into carbonic acid (H_2CO_3), reducing the amount of bicarbonate filtered by the kidney. In addition, acidosis increases renal tubular H^+ secretion, which promotes bicarbonate reuptake and further reduces renal bicarbonate loss.

(Choice C) This patient's volume depletion and resulting hypotension reduce renal perfusion pressure, leading to increased renin release by the renal juxtaglomerular cells.

(Choice D) Acute tubular necrosis is characterized by progressively increasing serum creatinine with epithelial cell casts and muddy brown granular casts seen on urinalysis. Acute tubular necrosis is unlikely in this patient with normal serum creatinine.

Educational objective:
Normally, metabolic acidosis is partially compensated for by respiratory alkalosis. When the steady-state $PaCO_2$ persists above the range given by the Winter formula ($PaCO_2 = [1.5 * HCO_3^-] + 8 \pm 2$), the patient has a superimposed respiratory acidosis (respiratory failure).

References

- Respiratory failure in diabetic ketoacidosis.

Pathophysiology	Endocrine, Diabetes & Metabolism	Metabolic acidosis
Subject	System	Topic

(chronic only*)	~4 mEq/L ↑ in bicarbonate per 10 mm Hg ↑ in $PaCO_2$
Respiratory a (chronic or	

*Compensation for resp
simplicity, normal baseli

The combination of acute-
ketoacidosis, which in thi
metabolic acidosis confirm
acetoacetate).

Patients with metabolic ac
helps mitigate the acidemi
Winter formula, where Pa
compensation.

This patient's serum HCO
expected, indicating that
can cause pulmonary ede
respiratory failure.

(Choice A) Acute adrena
hyperchloremic acidosis.

(Choice B) Ketoacidosis
(H_2CO_3), reducing the am
bicarbonate reuptake and

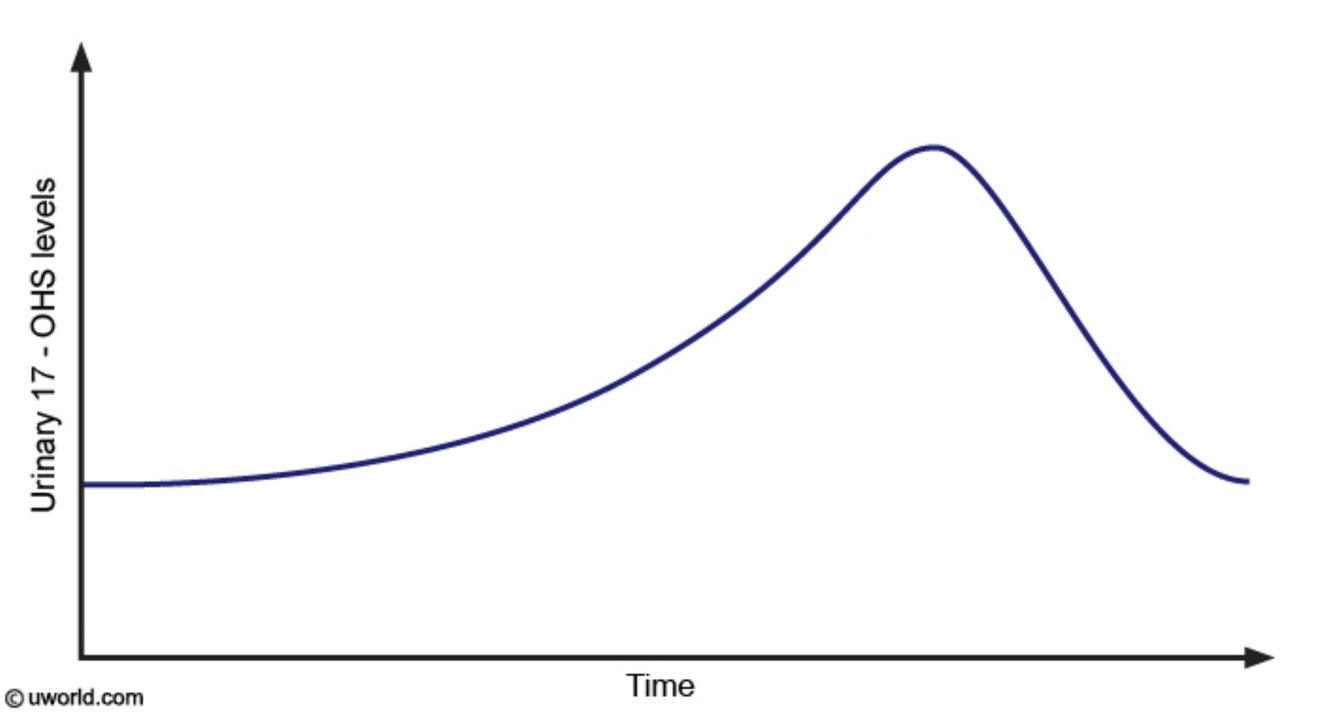
(Choice C) This patient's volume depletion and resulting hypotension reduce renal perfusion pressure, leading to increased renin release by the renal juxtaglomerular cells.

Exhibit Display

Anion gap metabolic acidosis	
Calculation	Anion gap = sodium – (chloride + bicarbonate) (Normal: 10-14)
Common causes Mnemonic: MUDPILES	• Methanol • Uremia • Diabetic ketoacidosis • Propylene glycol/paraldehyde • Isoniazid/iron • Lactic acidosis • Ethylene glycol (antifreeze) • Salicylates (aspirin)

Add To New Card | Existing Card

A 60-year-old woman is being evaluated for chronic weakness and fatigue. She has no other medical problems and takes no medications. After performing initial laboratory studies, the physician decides to proceed with a metyrapone stimulation test. The changes in urinary 17-hydroxycorticosteroid (17-OHS) excretion following metyrapone administration are shown in the graph below.

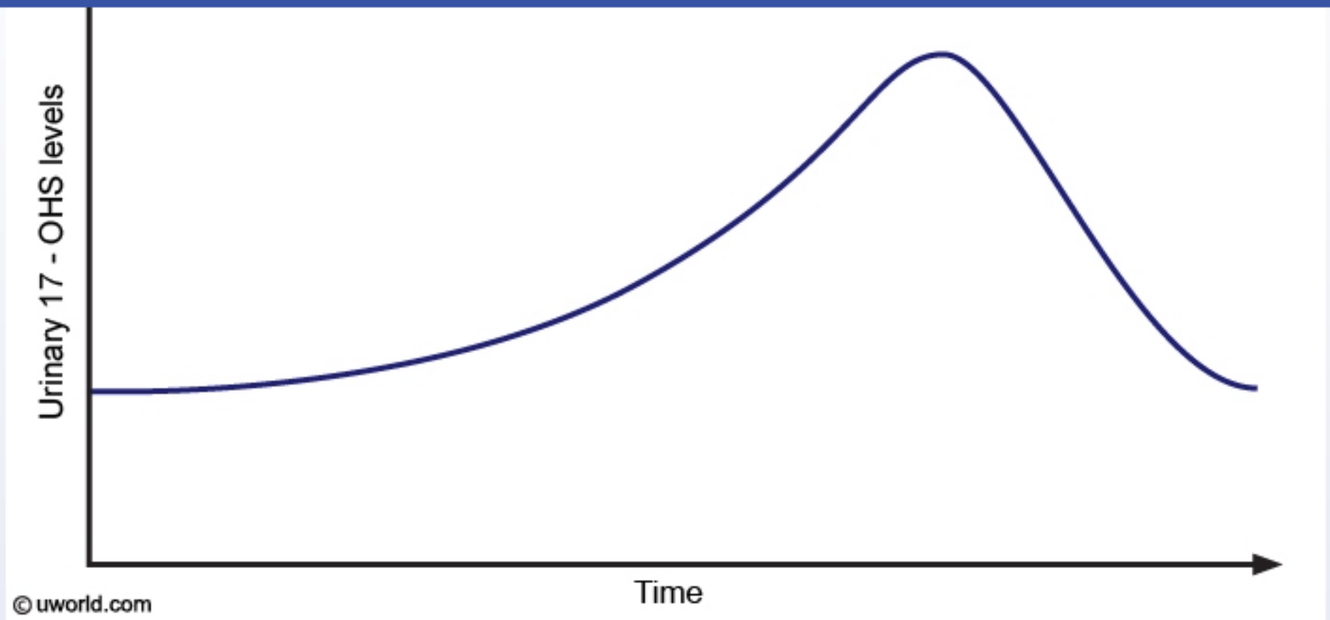


Which of the following mechanisms is most likely responsible for the findings seen in the graph?

A. ACTH surge

B. Aldosterone overproduction

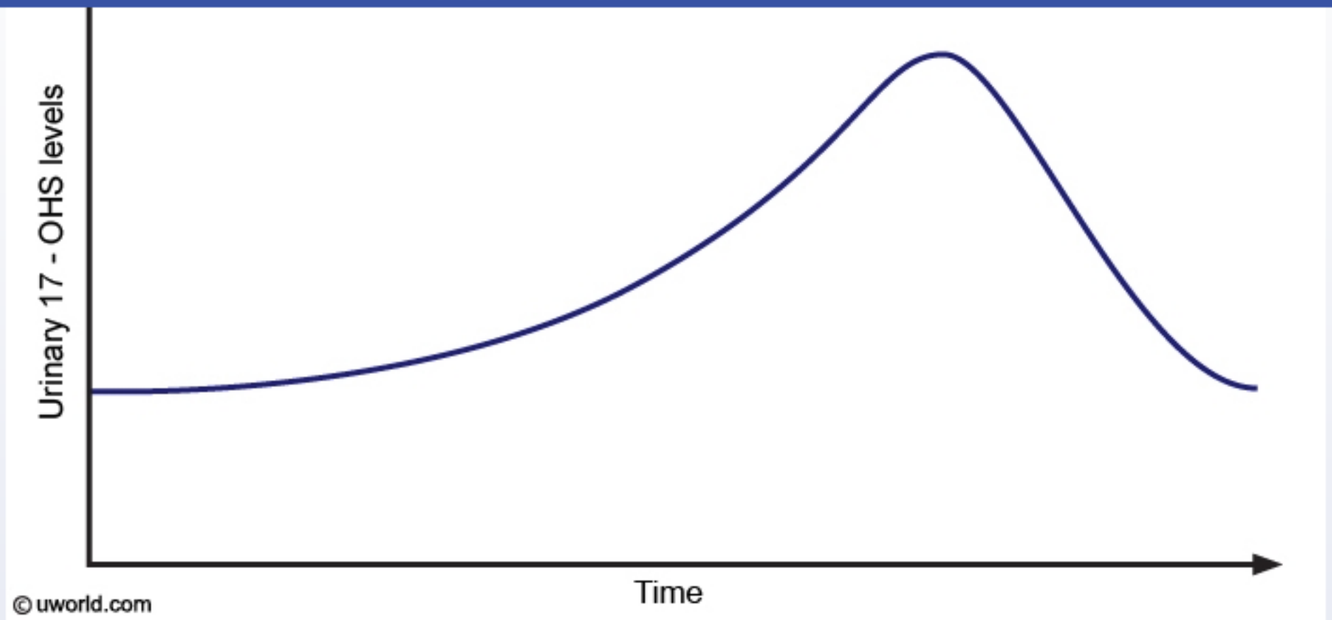
C. Cortisol overproduction



Which of the following mechanisms is most likely responsible for the findings seen in the graph?

- A. ACTH surge
- B. Aldosterone overproduction
- C. Cortisol overproduction
- D. Renin surge
- E. Vasopressin overproduction

Submit



Which of the following mechanisms is most likely responsible for the findings seen in the graph?

- ✓ A. ACTH surge (63%)
- B. Aldosterone overproduction (8%)
- C. Cortisol overproduction (23%)
- D. Renin surge (2%)
- E. Vasopressin overproduction (1%)

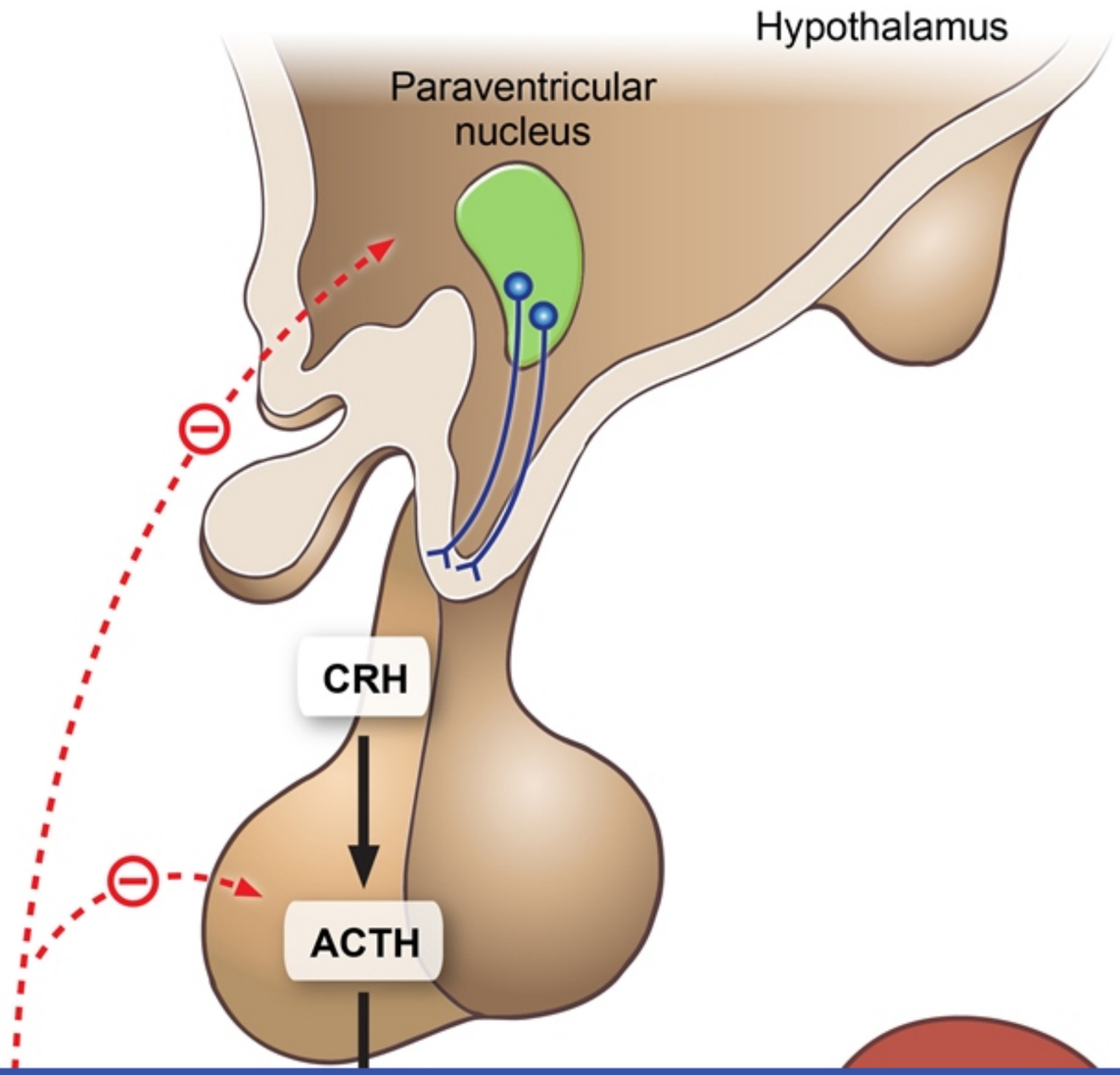
Omitted
Correct answer

63%
Answered correctly

05 secs
Time Spent

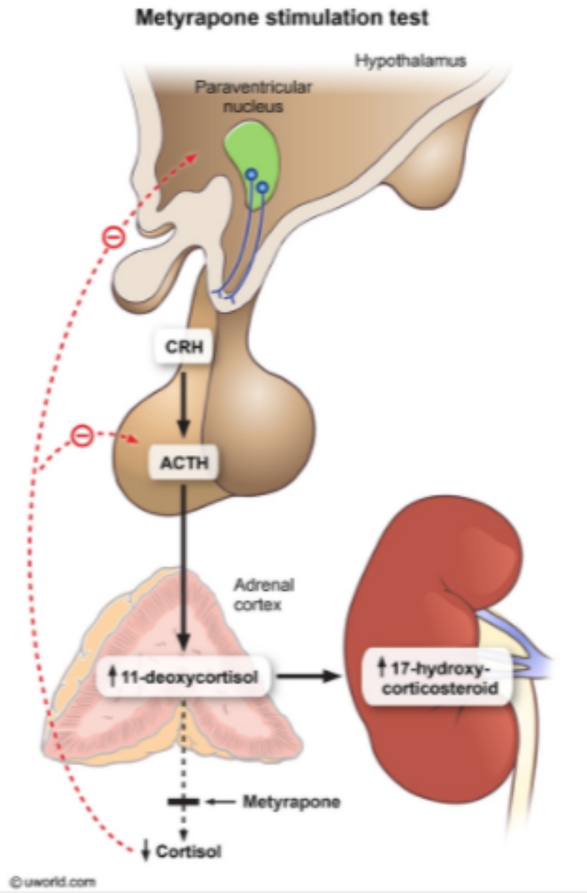
04/19/2020
Last Updated

Metyrapone stimulation test

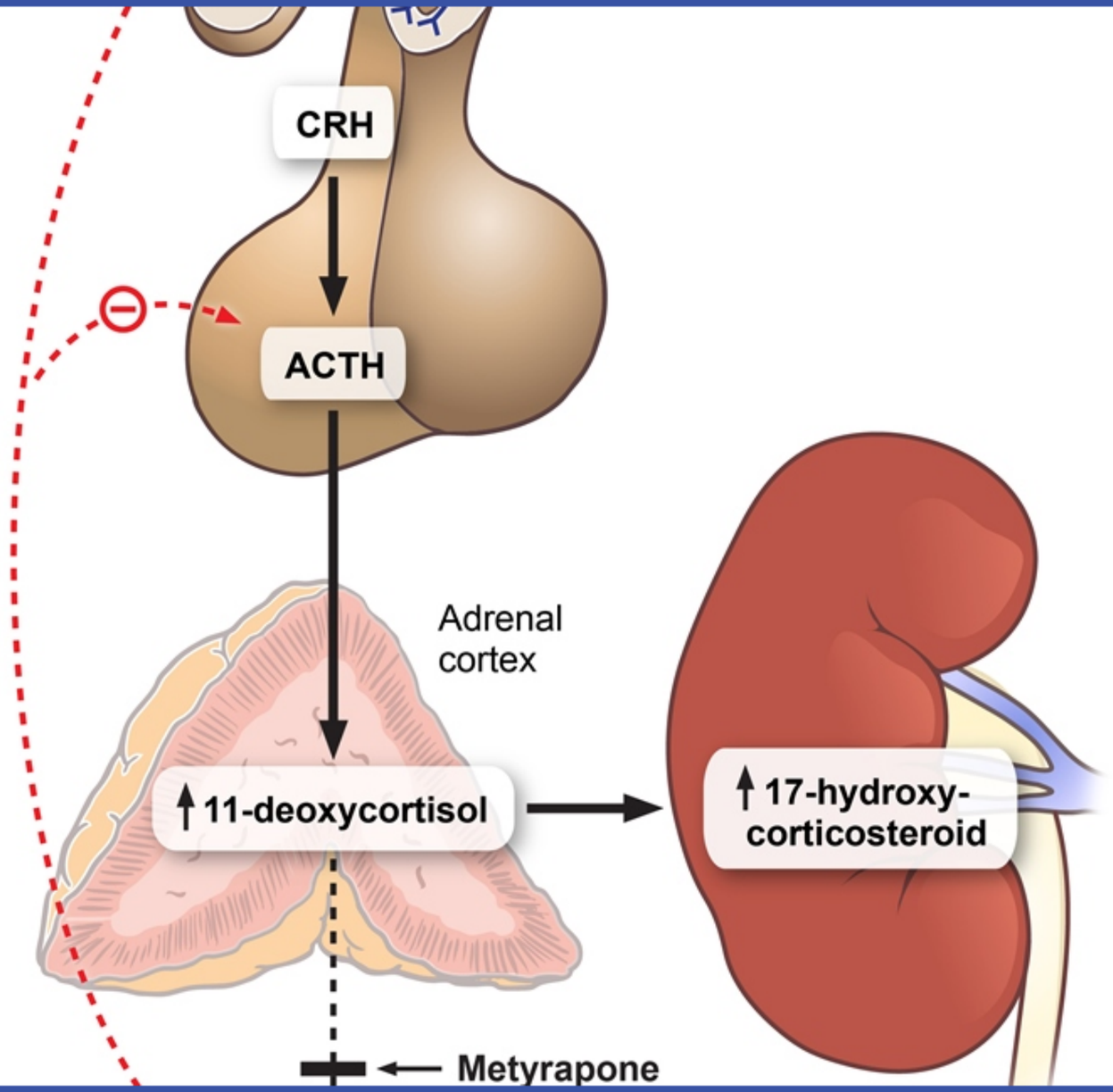


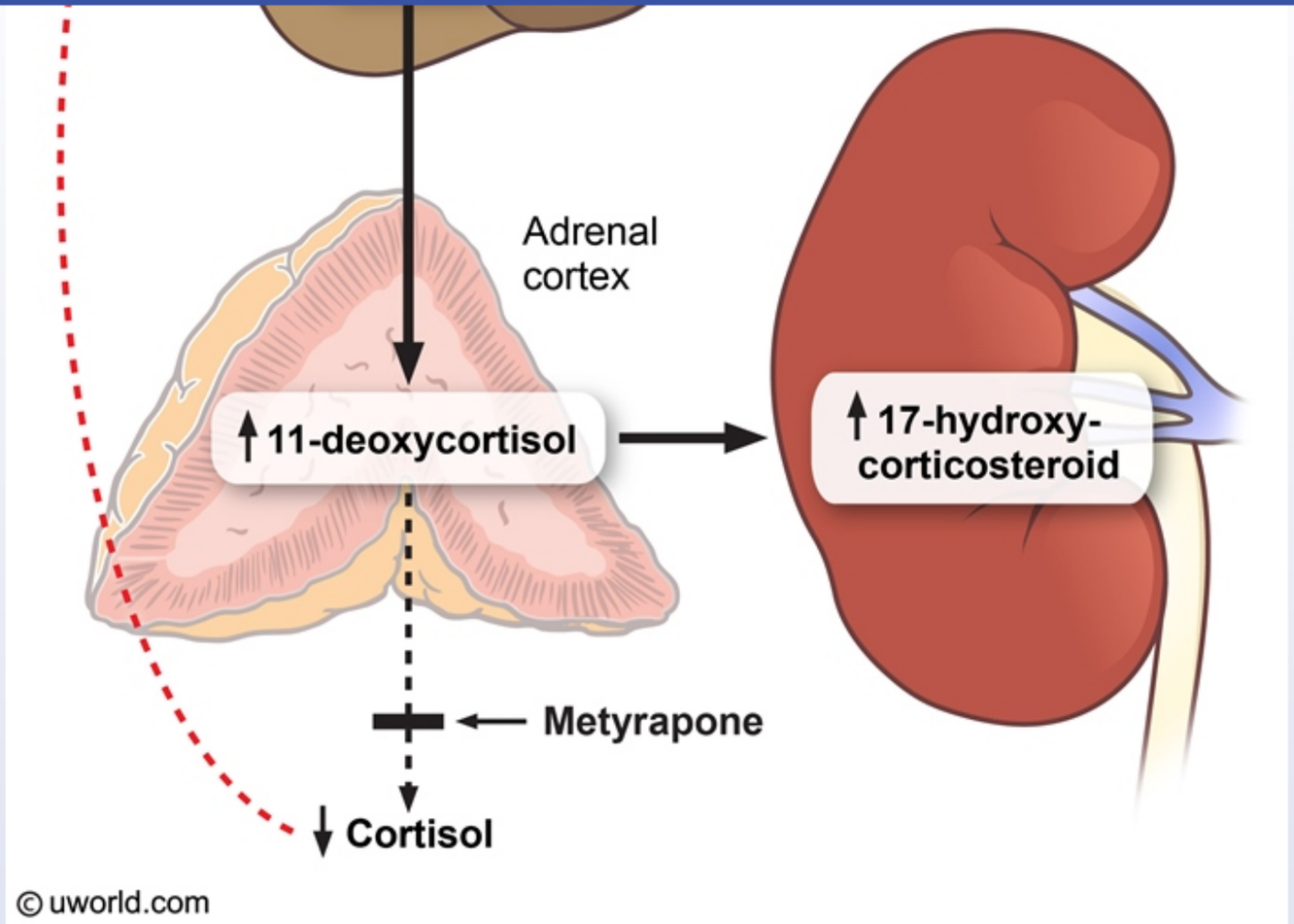
Metyrapone stimulation test

Exhibit Display



Zoom In | Zoom Out | Reset | Add To New Card | Existing Card


CRH
ACTH
Adrenal cortex
↑11-deoxycortisol
↑17-hydroxy-corticosteroid
Metyrapone



Like most hormones, secretion of cortisol is regulated via a negative feedback loop. Corticotropin-releasing hormone (CRH) is secreted by the hypothalamus in response to stress and circadian signals received from other parts of the central nervous system. CRH stimulates ACTH release by the pituitary, which in turn increases cortisol secretion by the adrenal cortex. High cortisol levels suppress secretion of ACTH and CRH, and low cortisol levels cause an increase in ACTH and CRH secretion.

Although not commonly used, the **metyrapone stimulation test** is a sensitive indicator of hypothalamic-pituitary-adrenal (HPA) axis integrity.

© uworld.com

Like most hormones, secretion of cortisol is regulated via a negative feedback loop. Corticotropin-releasing hormone (CRH) is secreted by the hypothalamus in response to stress and circadian signals received from other parts of the central nervous system. CRH stimulates ACTH release by the pituitary, which in turn increases cortisol secretion by the adrenal cortex. High cortisol levels suppress secretion of ACTH and CRH, and low cortisol levels cause an increase in ACTH and CRH secretion.

Although not commonly used, the **metyrapone stimulation test** is a sensitive indicator of hypothalamic-pituitary-adrenal (HPA) axis integrity. Metyrapone blocks cortisol synthesis by inhibiting **11-β-hydroxylase**, which converts **11-deoxycortisol to cortisol** in the zona fasciculata. Because 11-deoxycortisol lacks glucocorticoid activity, it does not inhibit pituitary ACTH secretion. As a result, the reduction in cortisol levels following metyrapone administration cause an increase in pituitary ACTH secretion. This leads to increased production of 11-deoxycortisol, which is further metabolized by the liver to **17-hydroxycorticosteroids** that accumulate in the urine.

Serum 11-deoxycortisol and urinary 17-hydroxycorticosteroid levels will normally rise in response to metyrapone, indicating an intact HPA axis. Failure of these steroid levels to increase implies primary or secondary adrenal insufficiency, which can be distinguished based on plasma ACTH levels.

(Choices B and D) The renin-angiotensin-aldosterone system regulates aldosterone synthesis by the zona glomerulosa. Because metyrapone inhibits 11-β-hydroxylase, aldosterone synthesis will decrease. However, accumulation of the aldosterone precursor 11-deoxycorticosterone (a weak mineralocorticoid) prevents the development of mineralocorticoid deficiency, so renin levels will not change significantly.

(Choice C) The inhibition of 11-β-hydroxylase by metyrapone would lead to a decrease in cortisol, not an increase.

(Choice E) Vasopressin is a hormone secreted by the posterior pituitary that is responsible for regulating water balance. Additionally, vasopressin acts as a potentiator for CRH, enhancing the release of ACTH. However, there is no clear feedback loop between cortisol and vasopressin; therefore, metyrapone administration is unlikely to lead to vasopressin overproduction.

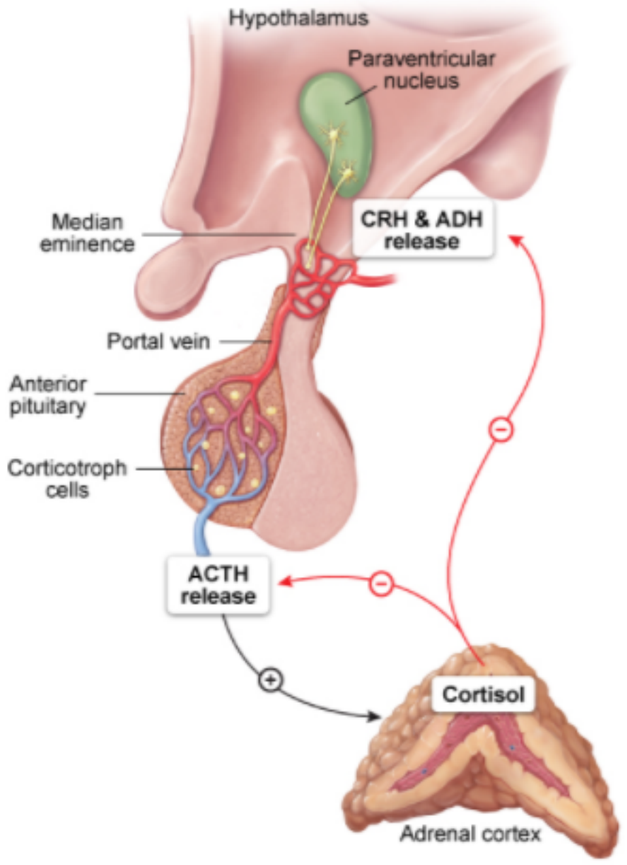
Educational objective:
Administration of metyrapone will cause a decrease in cortisol synthesis via inhibition of 11-β-hydroxylase. In patients with an intact hypothalamic-pituitary-adrenal axis, this will cause a reactive increase in ACTH, 11-deoxycortisol, and urinary 17-hydroxycorticosteroid levels.

Pathophysiology Endocrine, Diabetes & Metabolism Adrenal insufficiency

© uworld.com

Exhibit Display

Hypothalamic-pituitary-adrenal axis



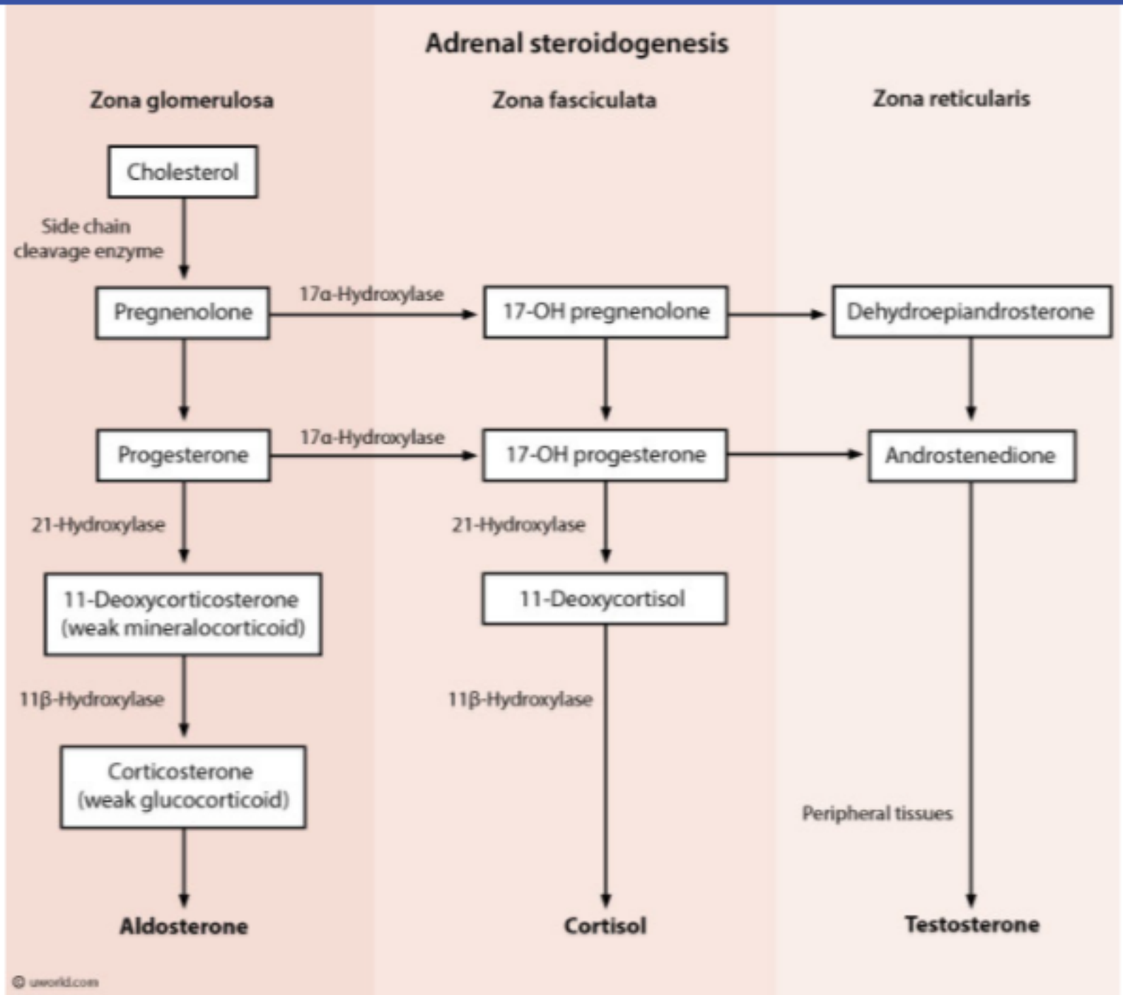
ADH = antidiuretic hormone; CRH = corticotropin-releasing hormone.
©UWorld

Zoom In | Zoom Out | Reset | Add To New Card | Existing Card

Pathophysiology | Endocrine, Diabetes & Metabolism | Adrenal insufficiency

© uworld.com

Exhibit Display



Zoom In | Zoom Out | Reset | Add To New Card | Existing Card

Pathophysiology | Endocrine, Diabetes & Metabolism | Adrenal insufficiency

A 21-year-old man comes to the office due to recent weight loss and fatigue. The patient is a college athlete and states, "My coach wants me to put on more weight, but I can't seem to do it. It doesn't matter how much I eat, I keep losing weight. I've been really thirsty and drinking lots of water lately too, and it's causing me to use the bathroom frequently during practice. I'm worried that I'm going to get dropped from the team if I don't get myself together." He is sexually active and has 1 lifetime partner. The patient's father was diagnosed with colon cancer at age 64. Which of the following studies would be the best next step to establish the diagnosis in this patient?

A. Colonoscopy
B. Hemoglobin A1c
C. HIV testing
D. Serum TSH level
E. Urinalysis
F. Urine drug screen

Submit

A 21-year-old man comes to the office due to recent weight loss and fatigue. The patient is a college athlete and states, "My coach wants me to put on more weight, but I can't seem to do it. It doesn't matter how much I eat, I keep losing weight. I've been really thirsty and drinking lots of water lately too, and it's causing me to use the bathroom frequently during practice. I'm worried that I'm going to get dropped from the team if I don't get myself together." He is sexually active and has 1 lifetime partner. The patient's father was diagnosed with colon cancer at age 64. Which of the following studies would be the best next step to establish the diagnosis in this patient?

A. Colonoscopy (1%)
✓ B. Hemoglobin A1c (62%)
C. HIV testing (0%)
D. Serum TSH level (12%)
E. Urinalysis (19%)
F. Urine drug screen (2%)

Omitted
Correct answer
B

62%
Answered correctly

02 secs
Time Spent

04/07/2020
Last Updated

Explanation

Type 1 diabetes mellitus	
Etiology	• Autoimmune destruction of pancreatic beta cells • **Insulin deficiency**

Type 1 diabetes mellitus	
Etiology	• Autoimmune destruction of pancreatic beta cells • **Insulin deficiency**
Signs & symptoms	• Polydipsia, polyuria • Polyphagia • Weight loss • Blurred vision • Ketoacidosis
Diagnosis	• **Fasting glucose** (≥126 mg/dL) • **Hemoglobin A1c** (≥6.5%) • Random glucose (≥200 mg/dL) • Oral glucose tolerance test

This patient's polyuria, polydipsia, fatigue, and weight loss despite increased food intake are suggestive of **type 1 diabetes mellitus**. Patients often develop these characteristic symptoms over an acute to subacute time frame and may occasionally present with diabetic ketoacidosis (nausea/vomiting, abdominal pain, decreased mental status, fruity odor to breath). Although most patients with type 1 diabetes mellitus are diagnosed before age 10, onset in adolescence and adulthood is not uncommon.

Appropriate initial tests and related diagnostic criteria for diabetes include:

- **Fasting plasma glucose ≥126 mg/dL**
- **Hemoglobin A1c ≥6.5%**
- **Random (nonfasting) glucose ≥200 mg/dL** in a patient with **symptoms** of hyperglycemia (eg, polyuria, polydipsia)
- Oral glucose tolerance test with plasma glucose ≥200 mg/dL 2 hours after glucose ingestion (preferred for diagnosis of gestational diabetes)

(Choice A) Colon cancer in a first-degree relative increases an individual's risk for this disease. However, because this patient's father was at an advanced age at diagnosis, the patient's risk is not significantly elevated.

This patient's polyuria, polydipsia, fatigue, and weight loss despite increased food intake are suggestive of **type 1 diabetes mellitus**. Patients often develop these characteristic symptoms over an acute to subacute time frame and may occasionally present with diabetic ketoacidosis (nausea/vomiting, abdominal pain, decreased mental status, fruity odor to breath). Although most patients with type 1 diabetes mellitus are diagnosed before age 10, onset in adolescence and adulthood is not uncommon.

Appropriate initial tests and related diagnostic criteria for diabetes include:

- **Fasting plasma glucose ≥126 mg/dL**
- **Hemoglobin A1c ≥6.5%**
- **Random (nonfasting) glucose ≥200 mg/dL** in a patient with **symptoms** of hyperglycemia (eg, polyuria, polydipsia)
- Oral glucose tolerance test with plasma glucose ≥200 mg/dL 2 hours after glucose ingestion (preferred for diagnosis of gestational diabetes)

(Choice A) Colon cancer in a first-degree relative increases an individual's risk for this disease. However, because this patient's father was at an advanced age at diagnosis, the patient's risk is not significantly elevated.

(Choice C) Acute HIV presents as an acute viral syndrome with nonspecific symptoms and signs (eg, weight loss, fatigue). However, polyuria and polydipsia suggest diabetes rather than acute HIV.

(Choice D) It is possible that weight loss and polyuria are due to thyrotoxicosis, but the absence of other symptoms of thyroid disease (eg, palpitations, heat intolerance, excessive sweating) makes this less likely.

(Choice E) Acute cystitis can cause frequent urination but the total urine volume is not increased, and polydipsia and weight loss are more suggestive of diabetes mellitus. Although urinalysis can detect glucosuria, it has low sensitivity for diabetes and should not be used to confirm the diagnosis.

(Choice F) Although surreptitious drug abuse can be considered in patients with weight loss or other unexplained symptoms, a hemoglobin A1c test is more likely to be diagnostic in light of this patient's polyuria and polydipsia.

Educational objective:
Type 1 diabetes mellitus typically presents subacutely with polyuria and polydipsia accompanied by fatigue and weight loss. The diagnosis can be confirmed with a fasting blood glucose or hemoglobin A1c measurement.

- Hemoglobin A1c ≥6.5%
- **Random (nonfasting) glucose ≥200 mg/dL** in a patient with **symptoms** of hyperglycemia (eg, polyuria, polydipsia)
- Oral glucose tolerance test with plasma glucose ≥200 mg/dL 2 hours after glucose ingestion (preferred for diagnosis of gestational diabetes)

(Choice A) Colon cancer in a first-degree relative increases an individual's risk for this disease. However, because this patient's father was at an advanced age at diagnosis, the patient's risk is not significantly elevated.

(Choice C) Acute HIV presents as an acute viral syndrome with nonspecific symptoms and signs (eg, weight loss, fatigue). However, polyuria and polydipsia suggest diabetes rather than acute HIV.

(Choice D) It is possible that weight loss and polyuria are due to thyrotoxicosis, but the absence of other symptoms of thyroid disease (eg, palpitations, heat intolerance, excessive sweating) makes this less likely.

(Choice E) Acute cystitis can cause frequent urination but the total urine volume is not increased, and polydipsia and weight loss are more suggestive of diabetes mellitus. Although urinalysis can detect glucosuria, it has low sensitivity for diabetes and should not be used to confirm the diagnosis.

(Choice F) Although surreptitious drug abuse can be considered in patients with weight loss or other unexplained symptoms, a hemoglobin A1c test is more likely to be diagnostic in light of this patient's polyuria and polydipsia.

Educational objective:
Type 1 diabetes mellitus typically presents subacutely with polyuria and polydipsia accompanied by fatigue and weight loss. The diagnosis can be confirmed with a fasting blood glucose or hemoglobin A1c measurement.

References

- Type 1 diabetes.

Pathophysiology	Endocrine, Diabetes & Metabolism	Diabetes mellitus
Subject	System	Topic

Copyright © UWorld. All rights reserved.

A 34-year-old man comes to the office due to a 6-month history of progressively worsening headaches. He has also noticed blurring of his peripheral vision while driving. The patient has no history of head injuries and has had no associated dizziness, weight change, diplopia, or polyuria. Medical history is unremarkable, and he takes no medications. He does not use tobacco, alcohol, or illicit drugs. Physical examination shows a bitemporal visual field deficit. Laboratory studies show a serum prolactin level >20 times the upper limit of normal. Cranial imaging reveals a large pituitary mass. Which of the following changes in serum GnRH, LH, and testosterone are most likely to be found in this patient?

	GnRH	LH	Testosterone
A.	↓	↓	↓
B.	↑	↓	↓
C.	↑	↑	↓
D.	↑	↑	↑
E.	↓	↓	↑

Submit

A 34-year-old man comes to the office due to a 6-month history of progressively worsening headaches. He has also noticed blurring of his peripheral vision while driving. The patient has no history of head injuries and has had no associated dizziness, weight change, diplopia, or polyuria. Medical history is unremarkable, and he takes no medications. He does not use tobacco, alcohol, or illicit drugs. Physical examination shows a bitemporal visual field deficit. Laboratory studies show a serum prolactin level >20 times the upper limit of normal. Cranial imaging reveals a large pituitary mass. Which of the following changes in serum GnRH, LH, and testosterone are most likely to be found in this patient?

	GnRH	LH	Testosterone
✓ A. (68%)	↓	↓	↓
B. (18%)	↑	↓	↓
C. (4%)	↑	↑	↓
D. (4%)	↑	↑	↑
E. (3%)	↓	↓	↑

Omitted
Correct answer
A

68%
Answered correctly

02 secs
Time Spent

01/17/2020
Last Updated

Explanation

Pituitary adenomas	
Cell type	**Clinical features of tumor**
Lactotroph (prolactin)	• Hypogonadism, infertility (men) • Galactorrhea, amenorrhea (women)
Corticotroph (ACTH)	• Cushing disease
Somatotroph (growth hormone)	• Acromegaly (adults) • Gigantism (children)
Thyrotroph (TSH)	• Thyrotoxicosis
Gonadotroph (LH, FSH)	• Nonfunctioning (hypopituitarism) • Mass effect

This patient's **bitemporal hemianopsia** and headaches suggest mass effect symptoms due to an expanding lesion near the optic chiasm. Cranial imaging (typically MRI scan) can confirm the diagnosis of a pituitary adenoma. Unlike other pituitary hormones, prolactin secretion is under negative regulation by dopamine from the hypothalamus, and any disruption of dopaminergic pathways in the pituitary stalk can cause a moderate increase in prolactin release. However, **very high prolactin levels**, as seen in this patient, suggest a prolactin-secreting adenoma (**prolactinoma**).

Increased circulating levels of prolactin suppress GnRH secretion, leading to a reduction in release of LH from the pituitary and decreased testicular testosterone production. In premenopausal women, prolactinomas typically present early with galactorrhea and amenorrhea. However, in men and postmenopausal women, early symptoms may be subtle and nonspecific (eg, decreased libido), and patients frequently present later with mass effect symptoms (eg, headache, visual field defects).

(Choices B and D) Physiologic GnRH secretion occurs in a pulsatile fashion and initiates gonadotropin (eg, LH, FSH) and subsequently

This patient's **bitemporal hemianopsia** and headaches suggest mass effect symptoms due to an expanding lesion near the optic chiasm. Cranial imaging (typically MRI scan) can confirm the diagnosis of a pituitary adenoma. Unlike other pituitary hormones, prolactin secretion is under negative regulation by dopamine from the hypothalamus, and any disruption of dopaminergic pathways in the pituitary stalk can cause a moderate increase in prolactin release. However, **very high prolactin levels**, as seen in this patient, suggest a prolactin-secreting adenoma (**prolactinoma**).

Increased circulating levels of prolactin suppress GnRH secretion, leading to a reduction in release of LH from the pituitary and decreased testicular testosterone production. In premenopausal women, prolactinomas typically present early with galactorrhea and amenorrhea. However, in men and postmenopausal women, early symptoms may be subtle and nonspecific (eg, decreased libido), and patients frequently present later with mass effect symptoms (eg, headache, visual field defects).

(Choices B and D) Physiologic GnRH secretion occurs in a pulsatile fashion and initiates gonadotropin (eg, LH, FSH) and subsequently testosterone secretion. However, prolonged, continuous GnRH secretion suppresses gonadotropins, resulting in lower levels of sex steroids. Long-acting GnRH agonists (eg, leuprolide) are used to suppress sex steroid–dependent diseases (eg, prostate cancer).

(Choice C) Primary hypogonadism with low testosterone levels results in loss of negative feedback on GnRH release, causing elevated levels of GnRH and LH.

(Choice E) Intake of exogenous testosterone (eg, anabolic steroid use) will suppress release of GnRH and subsequently LH.

Educational objective:
Large prolactin-secreting pituitary tumors can compress the optic chiasm, causing bitemporal hemianopsia. In addition, elevated prolactin levels suppress release of GnRH, leading to decreased LH secretion and subsequently impaired testosterone production in men.

References

- Pituitary adenomas: an overview.

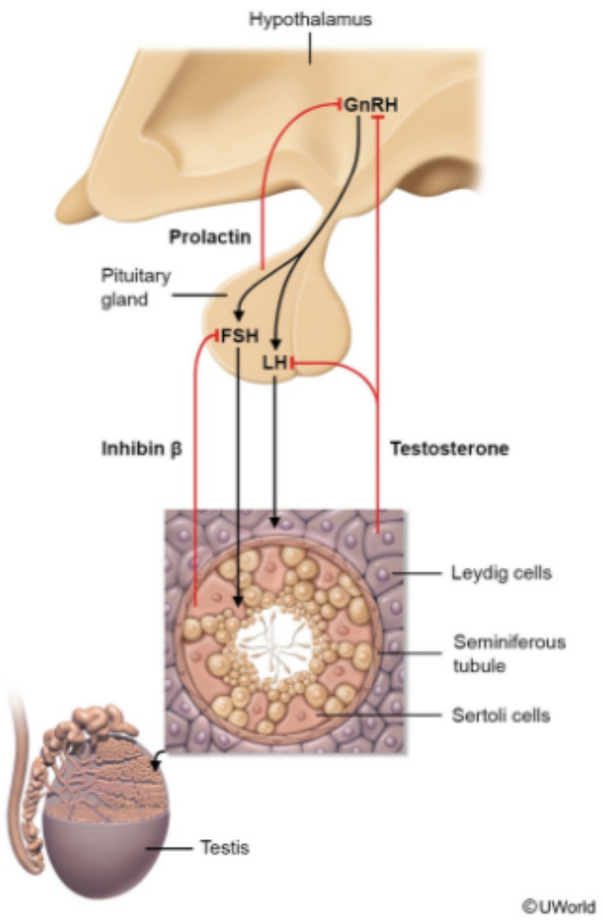
Pathophysiology	Endocrine, Diabetes & Metabolism	Pituitary adenoma
Subject	System	Topic

Copyright © UWorld. All rights reserved.

This patient's **bitemporal hemianopsia** and headaches suggest mass effect symptoms due to an expanding lesion near the optic chiasm. Cranial

Exhibit Display

Prolactin and gonadotropin production



Zoom In | Zoom Out | Reset | Add To New Card | Existing Card

A 25-year-old woman comes to the office due to excessive facial hair growth that has worsened over the past several years. The patient is very concerned and says it makes her feel self-conscious in public. She has tried several cosmetic measures, including laser removal and waxing, but the results have been unsatisfactory. Her past medical history is insignificant, and she takes no medications. The patient's last menstrual period was 6 weeks ago, but she regularly has long cycles and otherwise feels well. She is sexually active with her boyfriend and uses condoms for contraception. Examination shows moderate obesity with mild hirsutism on the face and chest. The patient is initiated on a combination oral contraceptive. Which of the following describes the primary mechanism by which this agent reduces hirsutism?

A. Blockade of ornithine decarboxylase
B. Decreased androgen production
C. Increased insulin sensitivity
D. Inhibition of 5-α-reductase
E. Inhibition of androgen receptors

Submit

A 25-year-old woman comes to the office due to excessive facial hair growth that has worsened over the past several years. The patient is very concerned and says it makes her feel self-conscious in public. She has tried several cosmetic measures, including laser removal and waxing, but the results have been unsatisfactory. Her past medical history is insignificant, and she takes no medications. The patient's last menstrual period was 6 weeks ago, but she regularly has long cycles and otherwise feels well. She is sexually active with her boyfriend and uses condoms for contraception. Examination shows moderate obesity with mild hirsutism on the face and chest. The patient is initiated on a combination oral contraceptive. Which of the following describes the primary mechanism by which this agent reduces hirsutism?

- A. Blockade of ornithine decarboxylase (0%)
- ✓ B. Decreased androgen production (80%)
- C. Increased insulin sensitivity (1%)
- D. Inhibition of 5-α-reductase (6%)
- E. Inhibition of androgen receptors (10%)

Omitted
Correct answer
B

80%
Answered correctly

02 secs
Time Spent

03/22/2020
Last Updated

Explanation

Polycystic ovary syndrome	
	• **Androgen excess**: Hirsutism, acne, androgenic alopecia

Polycystic ovary syndrome	
Clinical features	• **Androgen excess**: Hirsutism, acne, androgenic alopecia • **Ovarian dysfunction**: Menstrual irregularity, polycystic ovaries • **Insulin resistance**: Acanthosis nigricans, glucose intolerance/diabetes, metabolic syndrome • **Obesity**
Treatment	• Weight loss • Combination hormonal contraceptives • Metformin (if hyperglycemia/diabetes)

©UWorld

Excessive male-pattern hair growth in a woman is called **hirsutism**. Hirsutism can be due to increased androgen production (eg, polycystic ovary syndrome, Cushing syndrome, ovarian and adrenal tumors), increased local conversion of testosterone to dihydrotestosterone (DHT), or higher sensitivity of hair follicles to DHT (eg, idiopathic hirsutism). With excessive androgen exposure, soft, non-pigmented villous hair changes to coarse pigmented terminal hair in androgen-dependent areas of the body (eg, face, chest, back). **Virilization** occurs with very high androgen levels and is characterized by clitoromegaly, increased muscularity, and voice deepening in addition to hirsutism.

The most common cause of hirsutism is **polycystic ovary syndrome** (PCOS), which is often associated with elevated androgen levels. Combination oral contraceptive pills (OCPs) are usually the first choice for treating hirsutism in PCOS. OCPs work by suppressing LH secretion from the pituitary, thereby decreasing ovarian androgen production. They also increase sex hormone-binding globulin synthesis by the liver, decreasing free testosterone levels.

(Choice A) Ornithine decarboxylase is involved in DNA stabilization and repair. Inhibition leads to decreased cell growth and increased apoptosis. Eflornithine is a topical ornithine decarboxylase inhibitor used to decrease the rate of facial hair growth.

(Choice C) Patients with PCOS who develop diabetes mellitus are usually treated with metformin, which increases insulin sensitivity. Metformin can also help normalize menses but would not improve hirsutism.

pigmented terminal hair in androgen-dependent areas of the body (eg, face, chest, back). **Virilization** occurs with very high androgen levels and is characterized by clitoromegaly, increased muscularity, and voice deepening in addition to hirsutism.

The most common cause of hirsutism is **polycystic ovary syndrome** (PCOS), which is often associated with elevated androgen levels. Combination oral contraceptive pills (OCPs) are usually the first choice for treating hirsutism in PCOS. OCPs work by suppressing LH secretion from the pituitary, thereby decreasing ovarian androgen production. They also increase sex hormone-binding globulin synthesis by the liver, decreasing free testosterone levels.

(Choice A) Ornithine decarboxylase is involved in DNA stabilization and repair. Inhibition leads to decreased cell growth and increased apoptosis. Eflornithine is a topical ornithine decarboxylase inhibitor used to decrease the rate of facial hair growth.

(Choice C) Patients with PCOS who develop diabetes mellitus are usually treated with metformin, which increases insulin sensitivity. Metformin can also help normalize menses but would not improve hirsutism.

(Choices D and E) Testosterone receptor antagonists (eg, spironolactone) are effective in suppressing androgen-dependent hair growth. 5-α-reductase inhibitors (eg, finasteride) decrease peripheral conversion of testosterone to DHT but are less effective than testosterone receptor antagonists in treating hirsutism. Both are strongly teratogenic.

Educational objective:
Male-pattern hair growth in a woman is called hirsutism; the most common cause is polycystic ovary syndrome. Combination oral contraceptive pills can treat hirsutism by suppressing pituitary LH secretion and subsequently decreasing ovarian androgen production.

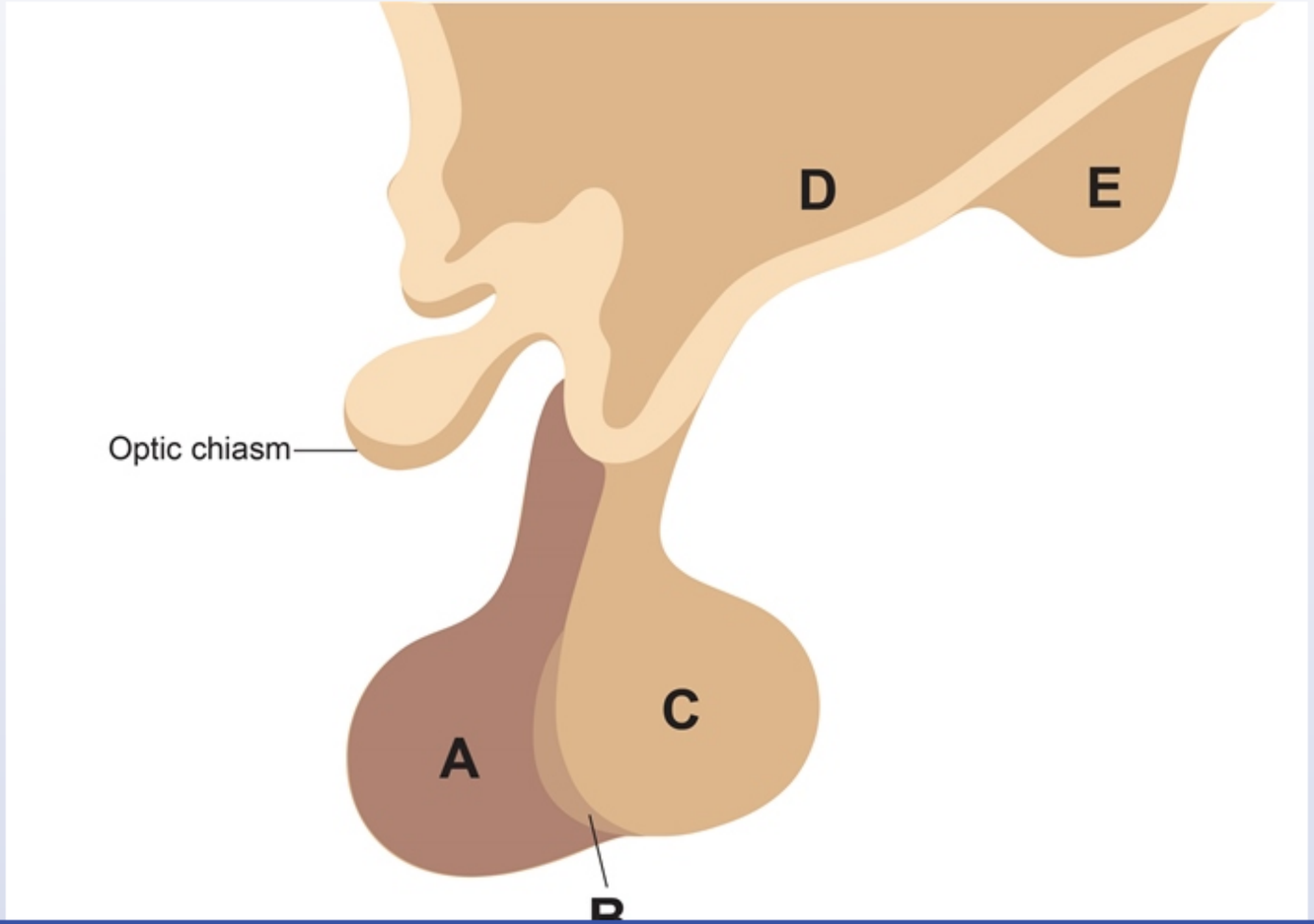
References

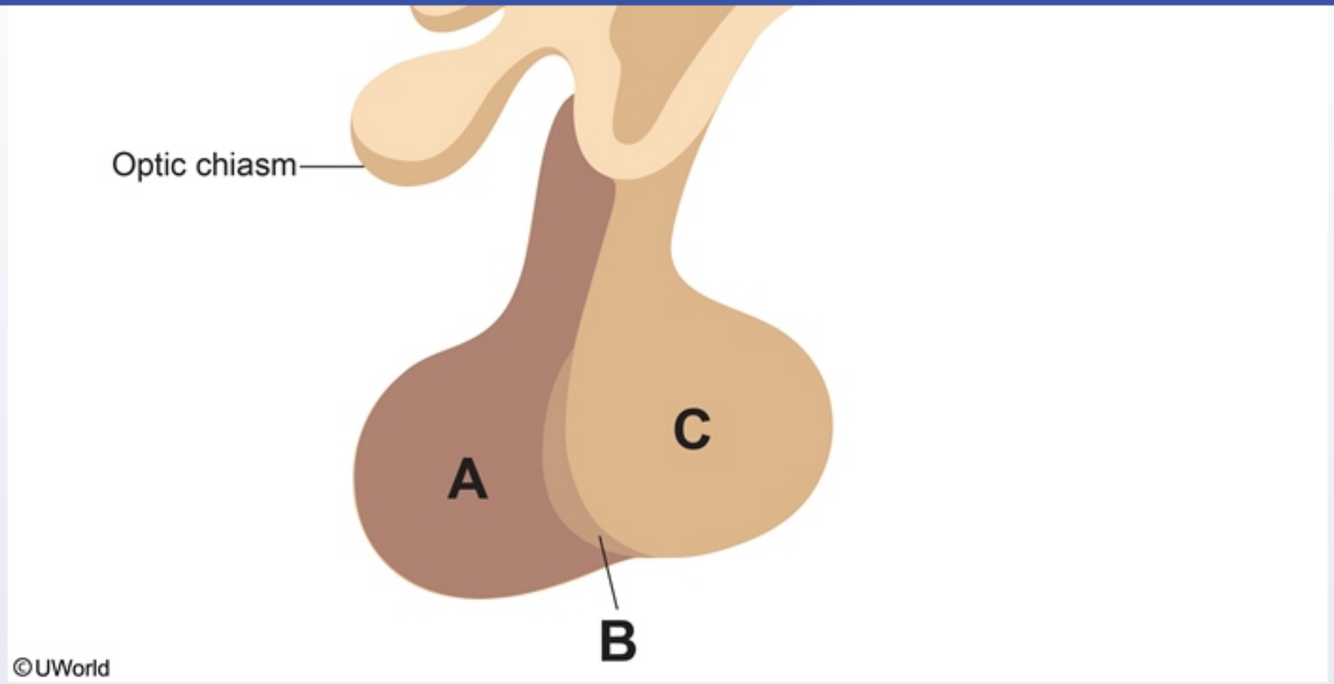
- Evaluation and treatment of hirsutism in premenopausal women: an endocrine society clinical practice guideline.
- Hirsutism in women.

Pathophysiology	Endocrine, Diabetes & Metabolism	Polycystic ovary disease
Subject	System	Topic

Copyright © UWorld. All rights reserved.

A 34-year-old woman comes to the clinic due to dizziness and mild confusion over the last week. The patient has a history of seizures beginning in childhood and was recently started on carbamazepine by her neurologist. Her temperature is 36.7 C (98 F), blood pressure is 121/72 mm Hg, pulse is 68/min, and respirations are 13/min. Physical examination is within normal limits. Laboratory studies show a low serum sodium concentration. It is determined that the patient's condition is caused by increased release of a hormone that is co-secreted with neurophysins. This hormone is most likely secreted into the circulation at which of the following sites?





A. A

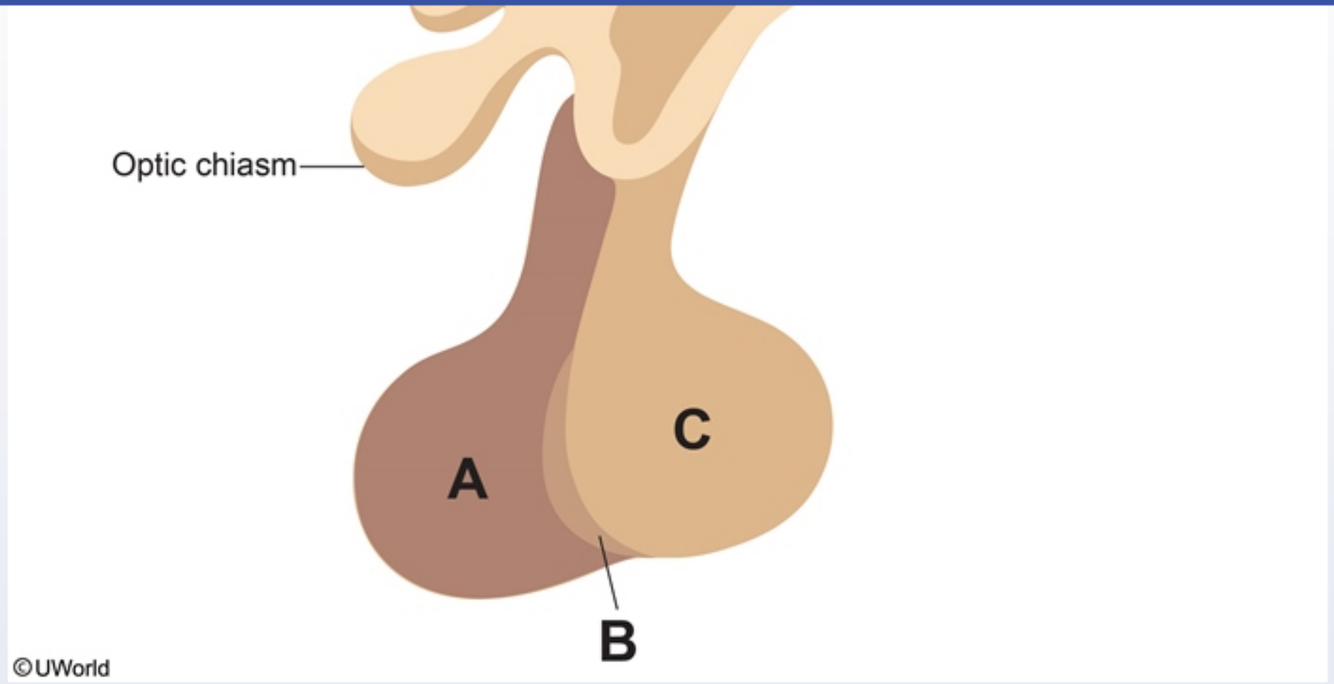
B. B

C. C

D. D

E. E

Submit



A. A (8%)

B. B (4%)

✓ C. C (78%)

D. D (7%)

E. E (1%)

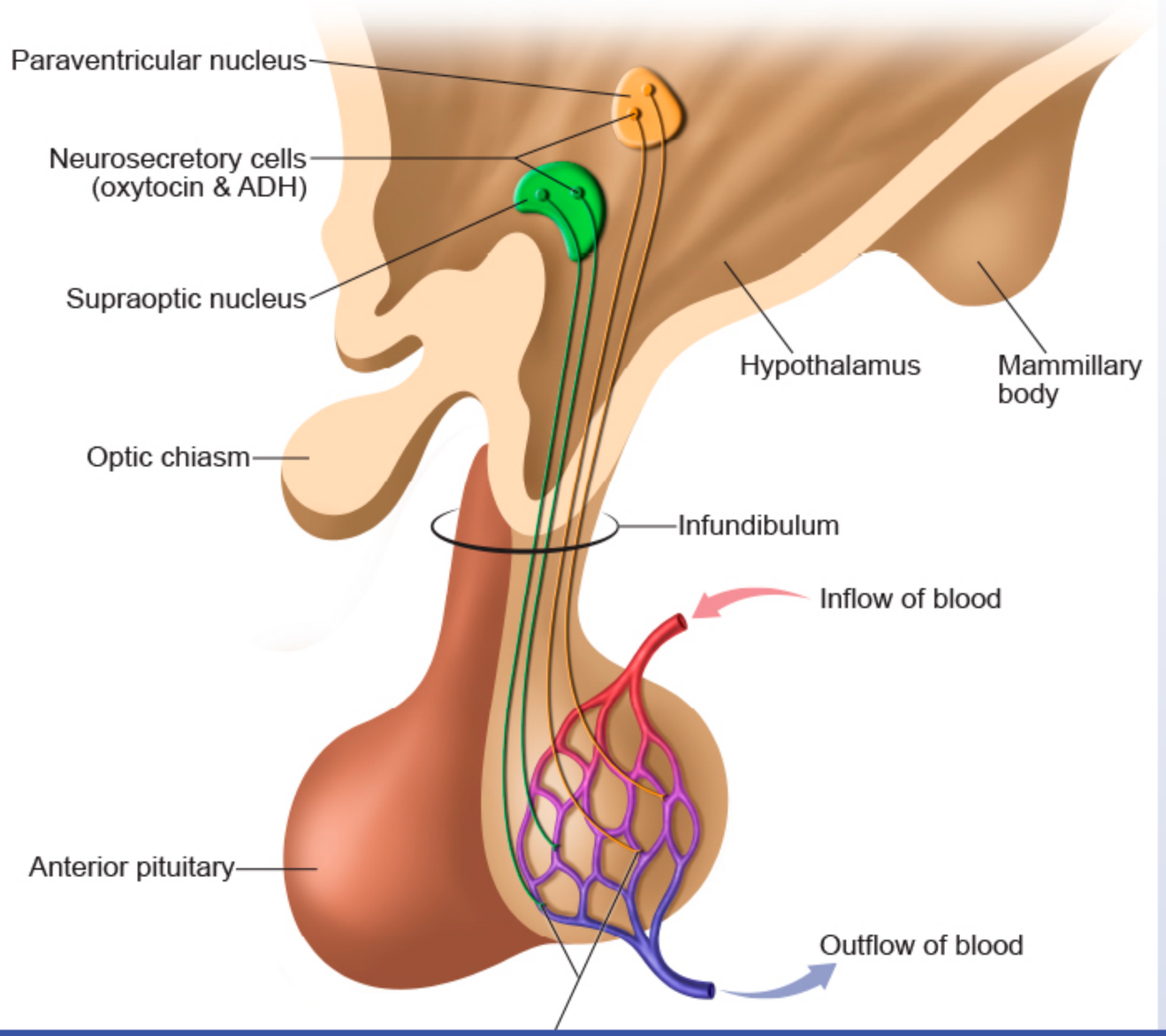
Omitted
Correct answer

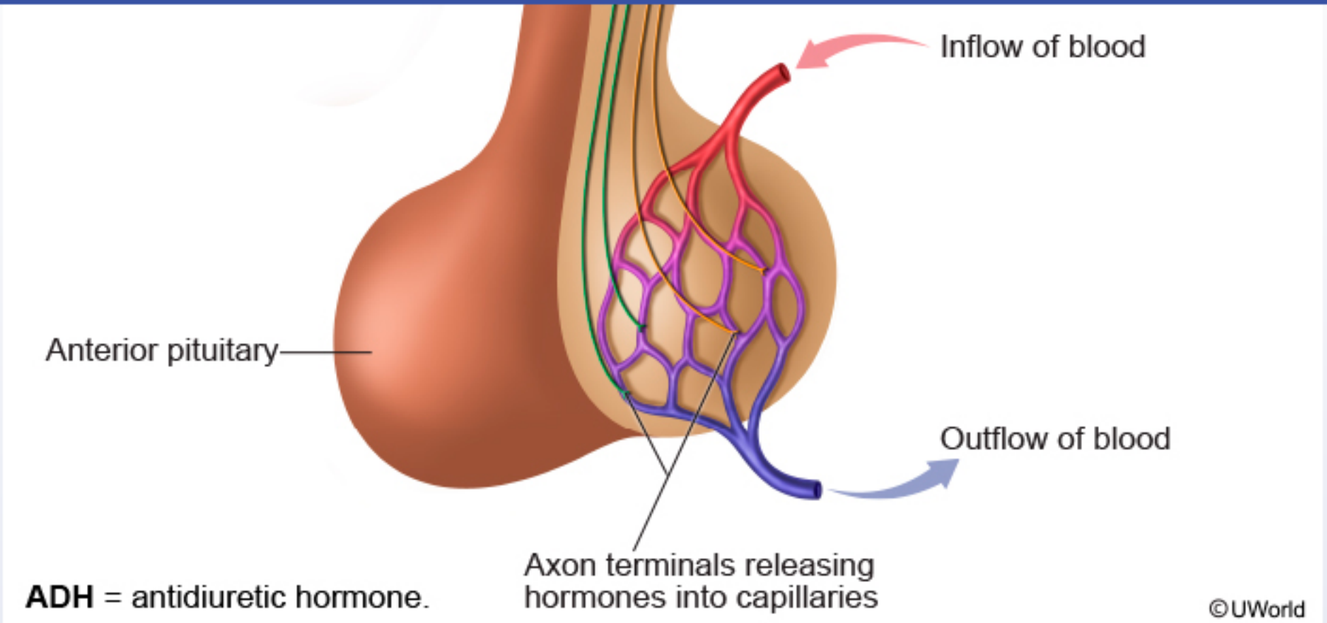
78%
Answered correctly

07 secs
Time Spent

01/13/2020
Last Updated

Neurohypophysis





This patient most likely has the syndrome of inappropriate antidiuretic hormone secretion (**SIADH**), which can be caused by a multitude of drugs, including **carbamazepine**, cyclophosphamide, and selective serotonin reuptake inhibitors.

Antidiuretic hormone (vasopressin) and oxytocin are **synthesized** within magnocellular neurons found in the supraoptic and paraventricular nuclei of the hypothalamus. Most magnocellular neurons produce either vasopressin or oxytocin. Once translated, these hormones are packaged into vesicles and travel via anterograde axonal transport to the posterior pituitary (neurohypophysis). There, the hypothalamic axons terminate into Herring bodies, which are specialized nerve terminals that act as storage sites for the secretory vesicles. These vesicles also contain proteins known as **neurophysins** that are involved in posttranslational hormone processing and stabilization during axonal transport. Vasopressin and oxytocin and their associated neurophysins are then **secreted** from the **posterior pituitary** into the hypophysial vein to enter the systemic circulation.

(Choice A) The anterior pituitary (adenohypophysis) is the glandular portion of the pituitary that lies closest to the optic chiasm. It is composed of various hormone-secreting cells, including somatotropes (growth hormone), lactotropes (prolactin), gonadotropes (FSH and LH), thyrotropes (TSH), and corticotropes (ACTH).

into vesicles and travel via anterograde axonal transport to the posterior pituitary (neurohypophysis). There, the hypothalamic axons terminate into Herring bodies, which are specialized nerve terminals that act as storage sites for the secretory vesicles. These vesicles also contain proteins known as **neurophysins** that are involved in posttranslational hormone processing and stabilization during axonal transport. Vasopressin and oxytocin and their associated neurophysins are then **secreted** from the **posterior pituitary** into the hypophysial vein to enter the systemic circulation.

(Choice A) The anterior pituitary (adenohypophysis) is the glandular portion of the pituitary that lies closest to the optic chiasm. It is composed of various hormone-secreting cells, including somatotropes (growth hormone), lactotropes (prolactin), gonadotropes (FSH and LH), thyrotropes (TSH), and corticotropes (ACTH).

(Choice B) This is the vestigial intermediate lobe of the pituitary gland, which is derived from the posterior wall of Rathke's pouch during embryonic development. It is not a significant source of secretory products in humans, but can secrete a small amount of melanocyte-stimulating hormone.

(Choices D and E) The posterior hypothalamus is involved in the control of sympathetic responses, including temperature regulation; the mammillary bodies are important for memory recall. These regions do not directly secrete hormones.

Educational objective:
Vasopressin and oxytocin are synthesized within neurons found in the paraventricular and supraoptic nuclei and are released into the circulation from axon terminals in the posterior pituitary. Neurophysins are involved in the posttranslational processing and stabilization of oxytocin and vasopressin within neurosecretory vesicles during transport to the posterior pituitary.

References

- Progressive decline of vasopressin secretion in familial autosomal dominant neurohypophyseal diabetes insipidus presenting a novel mutation in the vasopressin-neurophysin II gene.

Pathophysiology	Endocrine, Diabetes & Metabolism	SIADH
Subject	System	Topic

Copyright © UWorld. All rights reserved.